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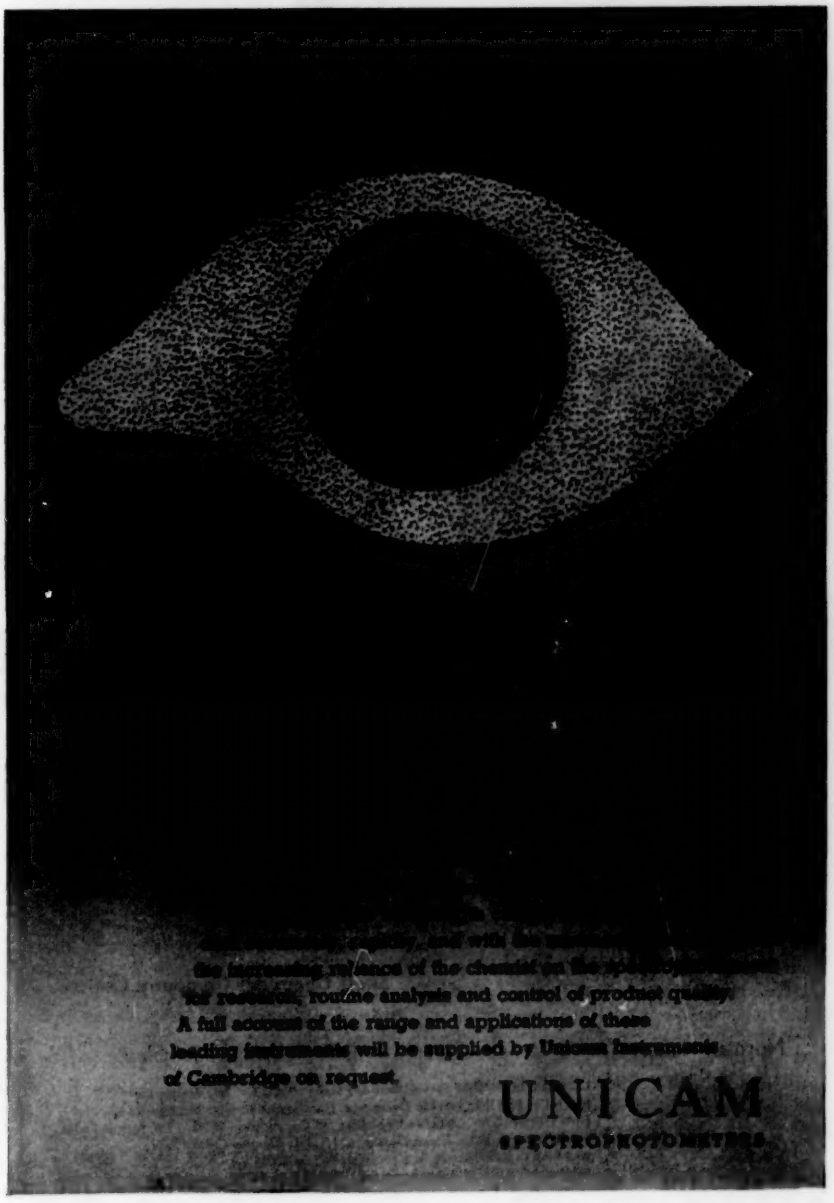
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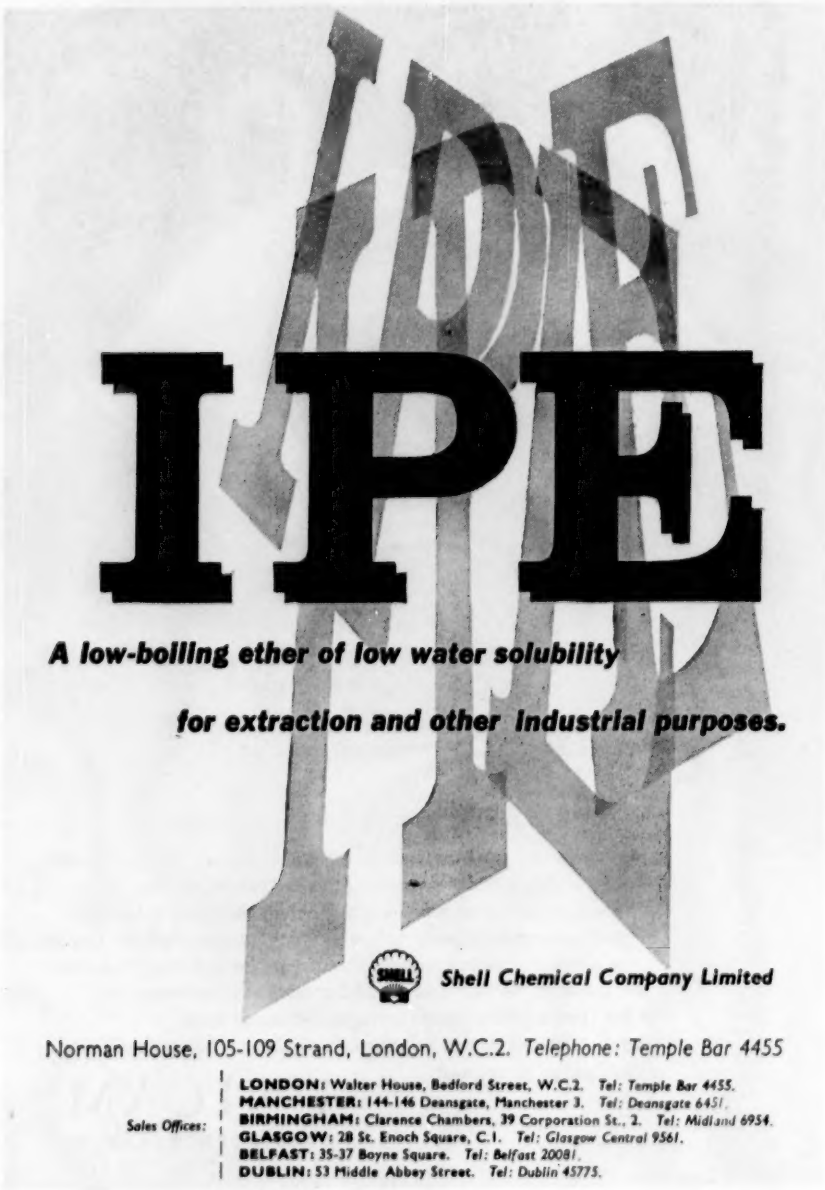
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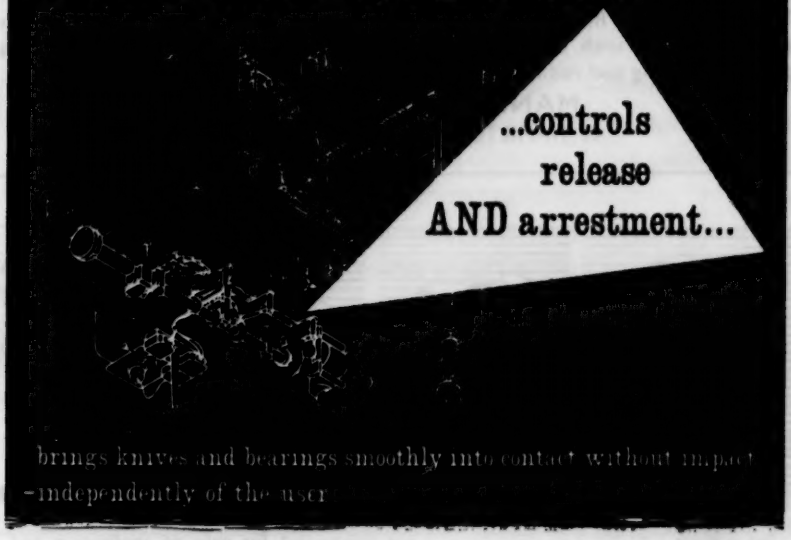

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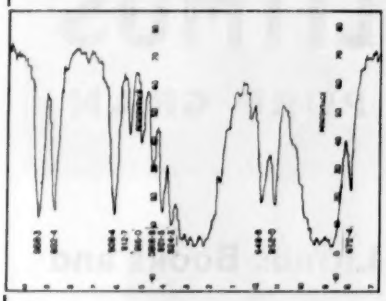

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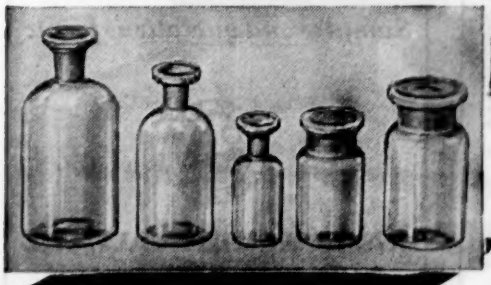

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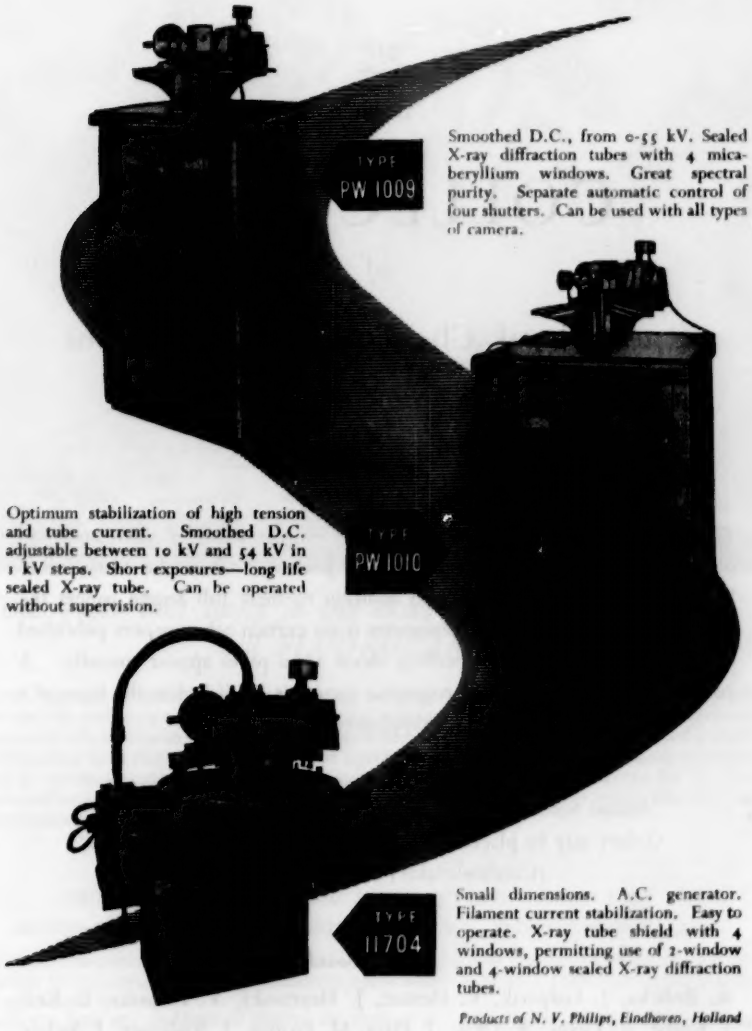

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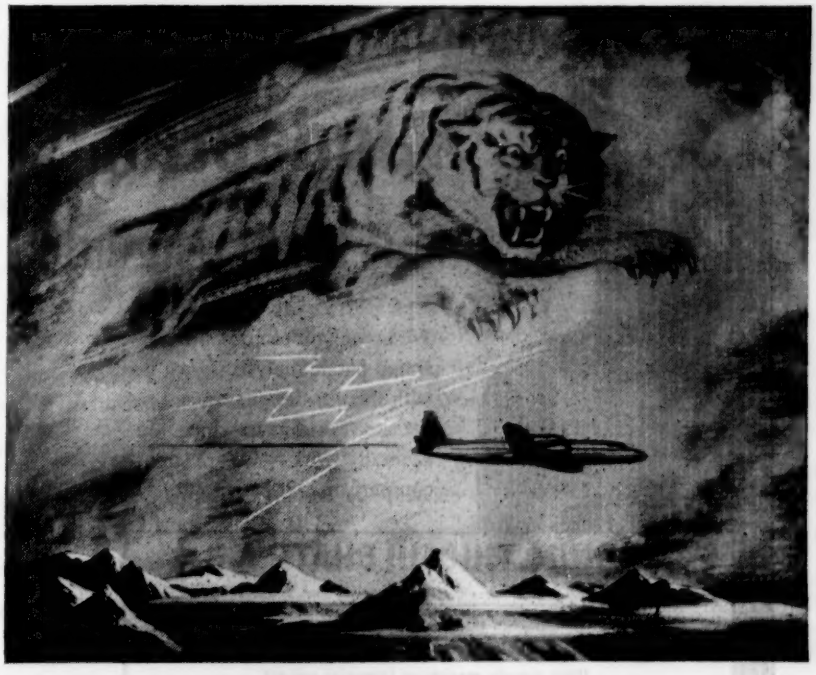

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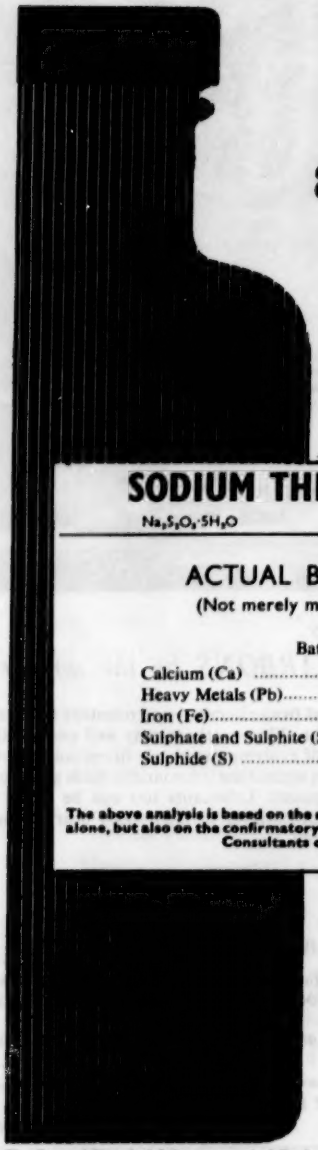

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Heavy Metals (Pb)	0·0004%
Iron (Fe)	0·0002%
Sulphate and Sulphite (SO_4)	0·001%
Sulphide (S)	no reaction

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Studies in Mycological Chemistry. Part III. Some Hydroxy- and Methoxy-benzenepolycarboxylic Acids.*

By JOHN C. ROBERTS.

[Reprint Order No. 6313.]

Syntheses of 3-hydroxybenzene-1 : 2 : 5-tricarboxylic acid and of 3-methoxy- and 3-hydroxy-benzene-1 : 2 : 4 : 5-tetracarboxylic acid are described. The evidence for their orientation is discussed and details of their chromatographic behaviour (on paper) are given.

THE three acids mentioned above, together with 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid, were required as reference compounds in connection with the identification of certain acids obtained by the oxidative degradation of purpurogenone, a metabolic product of *Penicillium purpurogenum* Stoll (see following paper).

Of these four acids, only one (the last mentioned) had previously been synthesised (Posternak, *Helv. Chim. Acta*, 1940, **23**, 1046; see also Groves, *J.*, 1954, 1817). Posternak obtained this acid by a two-stage oxidation of the substituted acetophenone prepared from 3 : 5-dimethylanisole and acetyl chloride (Friedel–Crafts reaction) (von Auwers and Borsche, *Ber.*, 1915, **48**, 1698). The somewhat unexpected orientation of this ketone had been established by the latter workers. The orientation of the Posternak acid is now confirmed for it has been shown that demethylation yields a hydroxybenzenetricarboxylic acid which gives an intense reddish-violet ferric reaction—proving the existence of one carboxyl group in an *ortho*-position to the hydroxy-group. The demethylation was achieved either by alkali fusion or by use of hydriodic acid.

A claim to have prepared 3-methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid (m. p. 250—251°) was made by Nikuni (*J. Agric. Chem. Soc. Japan*, 1941, **17**, 779; *Chem. Abs.*, 1942, **36**, 4814) who obtained the acid by oxidative degradation of methylated α-sorigenin. (α-Sorigenin is the aglycone of α-sorinin which is found in the bark of *Rhamnus japonica*.) A full account of this work is not available to us but it appears that the orientation of this acid was not rigorously proved. 3-Methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid (m. p. 249—251°) has now been synthesised by a route which leaves no doubt as to its orientation, and the similarity of its physical properties to those of Nikuni's acid indicates that the latter was correctly orientated. The acid was synthesised from 2 : 6-bishydroxymethyl-3 : 5-dimethylphenol, the orientation of which has been convincingly proved by Finn, Lewis, and Megson (*J. Soc. Chem. Ind.*, 1950, **69**, 129). Finn *et al.* (*loc. cit.*) describe the methylation and oxidation of this compound to 2-methoxy-4 : 6-dimethylbenzene-1 : 3-dicarboxylic acid but, in our hands, their method proved unsatisfactory. An improved procedure is described below. Finally, the dicarboxylic acid was oxidised, by alkaline potassium permanganate solution, to the desired tetracarboxylic acid. An attempt to synthesise the latter acid by chromic acid oxidation of durenyl acetate by the Fischer–Gross method (*J. prakt. Chem.*, 1911, **84**, 369, 372) was unsuccessful. Demethylation of the acid (by means of hydriodic acid) led to 3-hydroxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid, together with other hydroxybenzenepolycarboxylic acids which had been produced by partial decarboxylation.

The two hydroxybenzenepolycarboxylic acids, mentioned above, are readily soluble in water but sparingly soluble in dilute 2—4N-hydrochloric acid and this property has been exploited for their isolation. Partial decarboxylation occurs somewhat readily when their aqueous solutions are boiled and undoubtedly accounts for the high equivalent weights (recorded below) which were determined by Pregl's method (Pregl and Grant, "Quantitative Organic Microanalysis," 5th English Ed., Churchill, London, 1951, p. 165).

The four benzenepolycarboxylic acids, considered here, may be run on paper chromatograms. A knowledge of their R_F values and of the colours of the "spots" formed when

* Part II, *J.*, 1955, 2782.

the chromatograms are sprayed with ferric chloride solution is a valuable aid in their identification (see following paper).

Experimental.

Chromatographic Procedure.—The method used was essentially that of Bate-Smith and Westall (*Biochim. Biophys. Acta*, 1950, **4**, 427). A previously determined suitable quantity of the acid, dissolved in acetone or ether, was spotted on a strip of Whatman's No. 1 paper. The (descending) solvent was either the upper layer formed by equilibrating *n*-butanol (40 c.c.), glacial acetic acid (10 c.c.), and water (50 c.c.) or the lower layer formed from *m*-cresol (50 c.c.), glacial acetic acid (2 c.c.), and water (48 c.c.). R_F values obtained with the former solvent are represented as R_F(b) and those with the latter solvent as R_F(c). The chromatograms were allowed to run for 16—26 hr. at 16—18°, were " dried off " in a current of air (followed by, in the case of the *m*-cresol solvent mixture, heating them in an oven at 100°), and were then sprayed with 1% (for the hydroxy-acids) or 2% (for the methoxy-acids) neutral, aqueous ferric chloride. The former acids yield spots of a red shade while the latter acids yield yellow-brown stains.

3-Methoxybenzene-1 : 2 : 5-tricarboxylic Acid.—This acid was prepared by Posternak's method (*loc. cit.*). It had R_F(b) 0·76.

3-Hydroxybenzene-1 : 2 : 5-tricarboxylic Acid.—(i) The foregoing acid (0·72 g.), acetic acid (15 c.c.), and hydriodic acid (*d* 1·7; 15 c.c.) were heated under reflux for 5 hr. Water (10 c.c.) was added and the volume of the mixed solvents was reduced, by gentle heating *in vacuo*, to *ca.* 2 c.c. in order to induce separation of the organic acid. To the cooled mixture, 2N-hydrochloric acid (3 c.c.) was added. The hydroxy-acid was filtered off, washed with 2N-hydrochloric acid (3 c.c.), and dried (0·45 g., m. p. 219—221°). Recrystallisation from hot 4N-hydrochloric acid yielded *3-hydroxybenzene-1 : 2 : 5-tricarboxylic acid* (0·36 g.) in microscopic prisms, m. p. 217—218° (effervescence) (Found: C, 47·7; H, 2·7%; equiv., 76·4. $C_9H_6O_7$ requires C, 47·8; H, 2·7%; equiv., 75·4). It had R_F(b) 0·61, R_F(c) 0·02. [Hydrobromic acid (*d* 1·49) alone, or mixed with glacial acetic acid was inefficient as a demethylating agent.] This hydroxy-acid is readily soluble in water or ethanol. Its aqueous solution gives an intense reddish-violet ferric reaction.

(ii) The same acid (but of inferior quality and in smaller yield) was prepared thus. The methoxy-acid (0·15 g.), potassium hydroxide (1 g.; pellets), and water (2 drops) were held at fusion point for 1 min. The cooled mass was dissolved in water and filtered through glass-wool. Acidification of the solution and ether-extraction yielded the hydroxy-acid (50 mg.) which was recrystallised by allowing its solution in ether–benzene to evaporate slowly. The yield was 18 mg. and the m. p. 213—215° (effervescence).

2 : 6-Bishydroxymethyl-3 : 5-dimethylanisole.—2 : 6-Bishydroxymethyl-3 : 5-dimethylphenol was prepared (yield, 41% of recrystallised material, m. p. 146°) by the method of Finn *et al.* (*loc. cit.*) who give m. p. 147—148°. This material (7·7 g.), anhydrous potassium carbonate (8·2 g.), methyl sulphate (4·9 c.c.), and dry acetone (120 c.c.) were heated under reflux for 17 hr. and the hot solution was filtered. The residue was extracted with boiling acetone (2 × 70 c.c.), and the potassium salts were discarded. The combined acetone solutions, when cooled, yielded 2 : 6-bishydroxymethyl-3 : 5-dimethylanisole (3·0 g.); a further 2·7 g. of material were obtained by concentrating the mother-liquor to 30 c.c. Recrystallisation of the combined crops from water gave 4·2 g. of material, m. p. 168°. Finn *et al.* give m. p. 166°.

2-Methoxy-4 : 6-dimethylbenzene-1 : 3-dicarboxylic Acid.—To a suspension of the foregoing material (3·92 g.) in 2N-sodium hydroxide (20 c.c.) was added a solution of potassium permanganate (6·63 g.) in water (100 c.c.) and the mixture was left, with occasional shaking, at room temperature for 3 hr. The mixture was then saturated with sulphur dioxide and, after the addition of concentrated hydrochloric acid (12 c.c.), was kept at −2° for 12 hr. The crude acid was collected and triturated with a saturated solution of sodium hydrogen carbonate (50 c.c.). The mixture was filtered (to remove *ca.* 0·2 g. of insoluble material), and, to the filtrate was added concentrated hydrochloric acid (10 c.c.) in order to precipitate the dicarboxylic acid (2·0 g.), m. p. 232—234° (effervescence). Finn *et al.* give m. p. 236°.

3-Methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic Acid.—To a warm (50°) solution of the foregoing dicarboxylic acid (0·34 g.) in 2N-sodium carbonate (3 c.c.) was added a warm solution of potassium permanganate (0·96 g.) in water (10 c.c.), and the combined solutions were heated on the steam-bath for 3 hr. The small excess of permanganate was destroyed by the addition of a few drops of methanol. The mixture was filtered whilst hot and the manganese dioxide

was thoroughly extracted and washed with boiling water. The combined filtrates and washings were evaporated to 6 c.c. and acidified (concentrated hydrochloric acid) to *ca.* pH 1. The solution, after 16 hr. at −2°, had deposited a mass of small, silky needles (0·19 g.) of an acid potassium salt. To a solution of this salt in water (1·5 c.c.) was added concentrated hydrochloric acid (10 drops), and the solution was left at −2° for 3 days. *3-Methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid* (80 mg.) separated as prisms, m. p. 249—251° (decomp.) after becoming yellow at *ca.* 200° (Found: C, 46·3; H, 2·85; OMe, 10·9%; equiv., 70·9. $C_{10}H_8O_8$·OMe requires C, 46·5; H, 2·85; OMe, 10·9%; equiv., 71·0). It had R_F(b) 0·61. This acid is easily soluble in water. Addition of ferric chloride to its aqueous solution produces a yellow colour which is followed, almost immediately, by the formation of a buff-coloured, flocculent precipitate.

In the above method it was difficult to judge the amount of hydrochloric acid which was required for the precipitation of the acid potassium salt from the solution of the acid in excess of alkali. An alternative method for isolating the acid (in superior yield but of slightly inferior quality) was as follows. The dicarboxylic acid (1·94 g.) was oxidised as described above and the filtrate and washings (from the manganese dioxide precipitate) were concentrated to 30 c.c. To the warm solution was added a large excess of concentrated hydrochloric acid (19 c.c. in all). The precipitation of the tetracarboxylic acid (1·62 g., m. p. 244—246°) was complete after 1 hr. at −2°. (Recrystallisation from boiling 3N-hydrochloric acid did not improve the quality of the product. Decarboxylation probably occurred.)

3-Hydroxybenzene-1 : 2 : 4 : 5-tetracarboxylic Acid.—The methoxy-acid (0·6 g.), acetic acid (10 c.c.), and hydriodic acid (*d* 1·7; 10 c.c.) were heated under reflux for 5 hr. (Dissolution was complete after 15 min.) To the cooled solution was added water (7 c.c.), and the volume of the solvents was reduced, by gentle heating *in vacuo*, to *ca.* 1·5 c.c. After the addition of 2N-hydrochloric acid (2·5 c.c.), the crude hydroxy-acid was filtered off and washed with 2N-hydrochloric acid (3 c.c.). An attempt to recrystallise this crude acid (0·3 g.) from boiling N-hydrochloric acid led to the separation of a product (30 mg.) which was shown by analysis (for carbon and hydrogen) and by chromatography to be a mixture of hydroxy-acids formed by partial decarboxylation of the desired hydroxybenzenetetracarboxylic acid. The mother-liquor was evaporated *in vacuo* to dryness and the residue (which was shown by chromatography to contain only traces of hydroxy-acids produced by partial decarboxylation) was recrystallised from twenty times its weight of hot 4N-hydrochloric acid, the solution having been heated to a minimum extent before filtration to remove the less soluble, partially decarboxylated products. *3-Hydroxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid* (yield *ca.* 10%) separated as small prisms (Found: C, 44·6; H, 2·15%; equiv., 69·5. $C_{10}H_6O_9$ requires C, 44·4; H, 2·25%; equiv., 67·5) which, when heated, became yellow at 172°; the main portion sublimed at 239° to give a deep-yellow, crystalline sublimate; the small residue finally melted at 310°. This acid had R_F(b) 0·29 and is readily soluble in water. Its aqueous solution gives a dark reddish-violet ferric reaction.

Oxidation of Durenyl Acetate.—*Durenyl acetate*, prepared from durenol and acetic anhydride (containing a trace of concentrated sulphuric acid), was recrystallised from warm aqueous acetic acid, to give plates, m. p. 78—79° (Found: C, 74·8; H, 8·2. $C_{12}H_{16}O_2$ requires C, 74·9; H, 8·4%). This material (0·6 g.) was readily oxidised in warm (60°) acetic acid–acetic anhydride by chromic anhydride (2·5 g.) but an attempt to isolate the hydroxybenzenetetracarboxylic acid led to only a trace of colourless crystalline material which gave a violet ferric reaction.

I thank Dr. H. Booth for a generous gift of durenol.

THE UNIVERSITY, NOTTINGHAM. [*Received, April 7th*, 1955.]

Studies in Mycological Chemistry. Part IV. Purpurogenone, a Metabolic Product of* Penicillium purpurogenum *Stoll.*

By John C. Roberts and C. W. H. Warren.

[Reprint Order No. 6314.]

Isolation of the pigment, purpurogenone, from the mycelium of a strain of *Penicillium purpurogenum* Stoll, is described. Its molecular formula ($C_{14}H_{12}O_5$) has been established. From a knowledge of its general properties and of the nature of several compounds obtained by its hydrolytic and oxidative degradation, it is suggested that purpurogenone is the dihydroxychromanobenzoquinone (V). A resemblance between purpurogenone and citrinin (IX) is pointed out.

Penicillium purpurogenum Stoll is a mould belonging to the *P. purpurogenum* series which, together with other related series belonging to the Biverticillata–Symmetrica group, comprise a number of moulds which are remarkable for their abundant pigment production. They are, in general, of ubiquitous distribution and are frequently found growing on decaying organic matter, or, in hot climates, on deteriorating equipment such as canvas tents (Raper and Thom, " A Manual of the Penicillia," Baillière, Tindall and Cox, London, 1949). So far as we are aware, only one report (Brenner, *Svensk bot. Tidskr.*, 1918, **12**, 91) on the pigments of *P. purpurogenum* (*sic*) has been published. Since this report is chemically insignificant, we decided, as a first measure, to investigate in detail the pigments of one selected member of this species. This paper records the isolation of, and structural investigations on, a pigment from *P. purpurogenum* Stoll (" C.B.S.").

This mould grew readily on Raulin–Thom medium and produced a red colour in the substrate and a mycelium which was deep-green or yellow-green with a dark-red reverse. No significant amount of colouring material could be isolated from the substrate and this was not further investigated. The dried and powdered mycelium was extracted successively with light petroleum, with ether, and with acetone. The only pure material which could be isolated from the first two extracts was ergosteryl palmitate. The dark, reddish-brown acetone extract always contained the major portion of the pigments and, occasionally, some mannitol. When the acetone concentrate was mixed with aqueous mineral acid, a dark-brown, amorphous precipitate was formed. This crude pigment, after having been washed with light petroleum, was purified *via* its sparingly soluble sodium salt. Even so, the partially purified material resisted all attempts at crystallisation and a chromatographic purification was always essential. Chromatography of this material (in benzene solution) on a column of anhydrous magnesium sulphate, elution of the brilliant red band with benzene, and evaporation of the solvent gave a dark-red substance which was usually crystalline and almost pure [m. p. 306° (decomp.)]. Recrystallisation from acetone then yielded the pure pigment in small, flat prisms [m. p. 310° (decomp.)] which, in bulk, possess a magnificent crimson colour. We propose the name purpurogenone for this substance.

Analysis of purpurogenone detected no elements other than carbon and hydrogen and gave a zero result for methoxyl groups (Zeisel). The molecular weight was found by cryoscopic and crystallographic methods, and the molecular formula was determined as $C_{14}H_{12}O_5$. The molecule contained one *C*-methyl group (Kuhn–Roth) and three active hydrogen atoms (Zerewitinow). In ultraviolet and in visible light a solution of purpurogenone in chloroform showed a very high absorption over a wide range of wavelengths. It is not possible to determine any optical activity in purpurogenone since its solutions, of even moderate concentrations, are so intensely coloured. An attempt to perform an electrometric titration of purpurogenone proved abortive. The only water-miscible solvent in which purpurogenone was appreciably soluble was dioxan and it was found that the glass-electrode behaved abnormally in presence of this solvent.

Purpurogenone is insoluble in water and in aqueous mineral acids but dissolves in concentrated sulphuric acid to produce an intense blood-red colour. When an ethereal

* Part III, preceding paper.

solution of purpurogenone is shaken with saturated aqueous sodium hydrogen carbonate, the pigment is removed from the ethereal layer and a brown, amorphous, sparingly soluble sodium salt remains suspended in the aqueous layer. It is possible to regenerate the pigment (unchanged) from the sodium salt. The reaction of purpurogenone with aqueous caustic alkali is remarkable. If the pigment is shaken with 2N-sodium hydroxide an intense, emerald-green colour is produced which changes (within twenty seconds) to blue and later (one minute) to deep purple. When the alkaline, purple solution is warmed with zinc dust the colour disappears but it reappears when the mixture is cooled and shaken with air. At first, we thought this test indicated purpurogenone to be a hydroxy-quinone but our conclusion was premature, for it was later found that it was not purpurogenone itself but a degradation product (produced by hydrolysis and oxidation) which yielded the positive test. Hydrogenation of purpurogenone in acetic acid solution (with palladised charcoal or platinic oxide as catalyst) led to the disappearance of the brilliant red colour and uptake of one mol. of hydrogen. When the solution containing the dihydropurpurogenone was exposed to air the red colour reappeared within a few minutes.

Attempts to prepare crystalline derivatives of the pigment met with little success. Purpurogenone did not condense with 2 : 4-dinitrophenylhydrazine. Methylation by diazomethane or methyl sulphate (in presence of acetone and anhydrous potassium carbonate) yielded intractable, brown, amorphous products. The pigment appeared to condense with *o*-phenylenediamine (in glacial acetic acid) to give a product which separated in fine, red needles but different samples, prepared in apparently identical ways, did not yield consistent analytical results. Acetic anhydride (in presence of a trace of perchloric acid) readily converted purpurogenone into a yellow product (m. p. 226°, after " crystallisation " from ethanol) which was amorphous but analytically pure, giving figures corresponding to a triacetate. All attempts to obtain this compound in a crystalline state failed. We are of the opinion that it is a mixture resulting from the simultaneous acetylation of two or three tautomeric forms of purpurogenone. Triacetylpurpurogenone is optically active. Attempts at reductive acetylation were unsuccessful.

A more detailed examination of the reaction between purpurogenone and aqueous caustic alkali revealed that this reagent readily caused extensive degradation. (Lack of this knowledge had previously caused very considerable difficulties in devising a technique for isolating the pure pigment from the original acetone extracts.) Formic acid (0·5 mol. per mol. of pigment) was isolated as one of the degradation products. The involatile products were separated by conventional methods and by chromatography (on a column of anhydrous magnesium sulphate) into at least five coloured substances. One of these was almost certainly established as being a 2-hydroxy-1 : 4-naphthaquinone. It was obtained crystalline (m. p. *ca.* 220°) and gave positive results in all the colour tests for this class of compound (see Experimental section). Furthermore, it yielded a yellow acetate whose absorption spectrum indicated that it was a 1 : 4-naphthaquinone derivative. This hydroxynaphthaquinone is being further investigated.

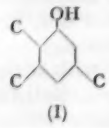
Oxidation of triacetylpurpurogenone by means of chromic acid in acetic acid–acetic anhydride (Fischer and Gross, *J. prakt. Chem.*, 1911, **84**, 372) gave a very poor yield of material which was shown (by paper chromatography) to be a mixture of two hydroxy-acids. One of these was almost certainly 3-hydroxybenzene-1 : 2 : 5-tricarboxylic acid, previously unknown (see Part III). The second acid was not identified but appeared to be identical with a product obtained as an intermediate during a graded oxidation of purpurogenone itself (see below and also Experimental section).

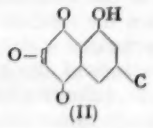
Purpurogenone was readily oxidised by hot nitric acid to a yellow product which was shown, by paper chromatography, to be very heterogeneous. None of the substances in the mixture could be identified.

When purpurogenone was oxidised under mild conditions with alkaline hydrogen peroxide there was obtained a moderate yield of a colourless, semi-crystalline acid which gave a blue ferric reaction and was chromatographically identical with the unidentified product resulting from the chromic acid oxidation of triacetylpurpurogenone. This oxidation product was methylated and then vigorously oxidised with potassium permanganate (in alkaline solution) to yield a crystalline acid, m. p. 252°. At first, this acid was

available to us only in minute quantity (1—2 mg.) and, from its chemical properties and physical constants, we thought it might have been 3-methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid (see Part III). However, we were later able to improve the yield in the graded degradation process, and the product was then conclusively identified as 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid. This acid had previously been obtained by Posternak (*Helv. Chim. Acta*, **1940**, **23**, 1046), first, as a degradation product of the anthraquinone pigment, roseopurpurin (from *P. roseopurpureum* Dierckx), and, secondly, by synthesis.

The identification of the degradation product, 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid, fixes the positions of nine of the fourteen carbon atoms in the purpurogenone molecule and establishes the partial structure (I). The observation that purpurogenone, by alkaline hydrolysis and aerial oxidation, produces a 2-hydroxy-1 : 4-naphthaquinone enables us to extend this to partial structure (II). The sensitivity of purpurogenone to aqueous


(I)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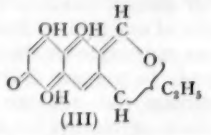
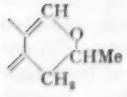
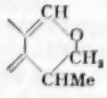
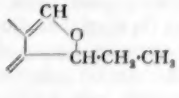
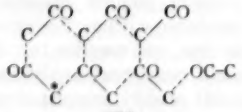

(III)


(III*a*)

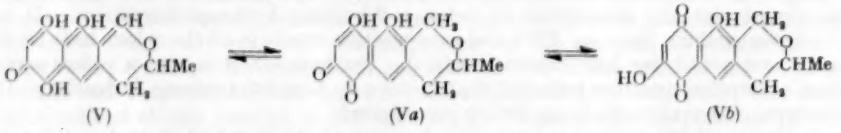

(III*b*)


(III*c*)

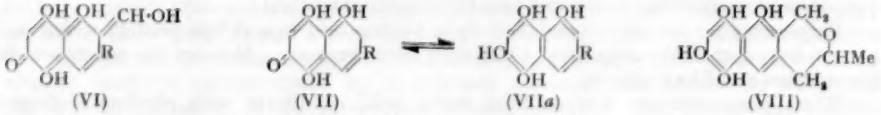

(IV)

solutions of strong alkalis and the expulsion of one carbon atom as formic acid by hydrolysis must now be taken into account and leads to partial structure (III). Finally, a *C*-methyl group has to be accommodated in the molecule. Since triacetylpurpurogenone is optically active, the *C*-methyl group in purpurogenone must be attached as in (III*a*, *b*, or *c*). The acetate rule of biosynthesis (Birch and Donovan, *Austral. J. Chem.*, **1953**, **6**, 360) favours the structure (III*a*) since the complete molecule (IV) may then be regarded as resulting from the " head-to-tail " condensation of seven acetate units followed by oxidation at the position C*.

We therefore suggest that purpurogenone should be represented by structure (V) or by the tautomeric structures (V*a*) and (V*b*).


(V) (V*a*) (V*b*)

Structure (V), which contains a vinylogous lactone system, readily accounts for the alkali-sensitivity of purpurogenone and for the nature of the products obtained when it is hydrolysed by aqueous alkali in presence of air. Such hydrolysis would be expected to yield initially a compound of structure (VI) which represents it as the enolic form of a vinylogous β-diketone. Further hydrolysis would lead to formic acid and a compound

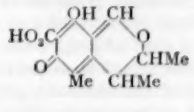

(VI) (VII) (VII*a*) (VIII)

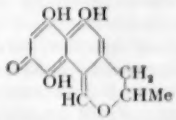
(R = $-CH_2 \cdot CHMe \cdot OH$)

represented by structure (VII) or by the tautomeric structure (VII*a*). Compounds of type (VII*a*) are known to undergo aerial oxidation (under alkaline conditions) readily, to give 2-hydroxy-1 : 4-naphthaquinones (Graebe, *Annalen*, **1870**, **154**, 303, 324).

Dihydropurpurogenone is formulated as (VIII).

In that purpurogenone contains a vinylogous lactone system, it bears a resemblance to the yellow pigment, citrinin (IX) (Hetherington and Raistrick, *Phil. Trans.*, 1931,

(IX) 

 (X)

220, *B*, 269; Coyne, Raistrick, and Robinson, *ibid.*, p. 297; Brown, Robertson, Whalley, and Cartwright, *J.*, 1949, **867**; Cartwright, Robertson, and Whalley, *ibid.*, p. 1563). In conclusion it should be pointed out that an alternative structure (X) for purpurogenone is in accord with all the observed facts. However, we prefer structure (V) on account of the generally accepted greater stability of the 2 : 6-naphthaquinone structure than of the 3 : 5-naphthaquinone structure.

Experimental

Paper Chromatography.—The methods employed and the significance of the terms R_F(b) and R_F(c) are described in Part III (preceding paper).

Isolation of Purpurogenone.—Penicillium purpurogenum Stoll, "C.B.S." (Centraalbureau voor Schimmelcultures, Baarn, Holland), was kept in sub-culture on Czapek–Dox agar slopes. For production of the pigment the mould was grown in surface culture on Raulin–Thom medium (see *Biochem. J.*, 1955, **59**, 480). Flat, round culture-flasks (see *ibid.*, 1944, **38**, 456), each filled with 500 c.c. of the medium, were sterilised and, after having been inoculated with a heavy, aqueous spore suspension, were kept at 28° ± 1° for *ca.* 3 weeks. The mycelium (from 140 flasks) was harvested, pressed free from surface liquid, allowed to drain for several hours, and finally dried *in vacuo* at 40°. The dry mycelium (*ca.* 250 g.) was ground to a fine, red-brown powder in a coffee-mill and was successively extracted (Soxhlet) with (i) light petroleum (b. p. 40—60°) for 48 hr., (ii) ether (48 hr.), and (iii) acetone (96 hr.).

The light-petroleum extract gave, on removal of the solvent, a liquid fat (3—5 g.), treatment of which with cold ethanol (95%; 50—75 c.c.) yielded a semi-crystalline substance which was filtered off, washed with ethanol, and then, after two crystallisations from ethanol, gave small, glistening prisms (0·65 g.), m. p. 104—106°. This material gave a strong Liebermann–Burchard test (red ⟶ violet ⟶ green) and was converted, by hydrolysis, into a sterol [fine needles, m. p. 159—161° (after two crystallisations from methanol) (Found: C, 81·3; H, 11·0. Calc. for $C_{28}H_{44}O$: C, 81·1; H, 11·1%)] and a fatty acid, m. p. 59—62° (after recrystallisation from aqueous methanol). It was thus identified as ergosteryl palmitate. Raistrick and Oxford (*Biochem. J.*, 1933, **27**, 1176) give m. p. 106—108° for this compound.

The ethereal extract contained fat, ergosteryl palmitate, and a small quantity of pigment which was not further investigated. From the dark, reddish-brown acetone extract, there occasionally separated a small quantity of long, colourless needles. These were collected, washed with acetone, and recrystallised from methanol to give mannitol (m. p. 166°; acetate, m. p. 121—122°).

The filtered acetone extract (*ca.* 1 l. from 250 g. of mycelium) was concentrated to 150 c.c., acidified with 4N-hydrochloric acid, and diluted with about four times its volume of water. The diluted mixture was left at room temperature for ½ hr. and the chocolate-brown precipitate, which had formed, was collected by filtration, washed with water, and dried *in vacuo*. This crude pigment (8—14 g.) was ground to a fine powder and exhaustively extracted (Soxhlet) with light petroleum (b. p. 40—60°) for *ca.* 8 hr. The powdered residue was heated under reflux with ether (3 l.). The cooled, deep-red ethereal solution was filtered from insoluble material (*ca.* 3 g. of a black powder) and extracted with a saturated, aqueous solution (2 × 400 and 1 × 200 c.c.) of sodium hydrogen carbonate (in this extraction vigorous shaking must be avoided, since intractable emulsions may occur). An amorphous, brown, very sparingly soluble sodium salt of the pigment was formed which remained suspended in the aqueous phase. The yellow-brown ethereal solution was discarded. The combined sodium hydrogen carbonate extracts and suspensions were washed with ether (2 × 250 c.c.) and then strongly acidified with 4N-hydrochloric acid. The liberated pigment was collected in chloroform (2 × 750 and 1 × 500 c.c.), and the combined chloroform solutions were washed with water, dried (Na_2SO_4), and filtered. The sodium sulphate was washed well with chloroform to remove adsorbed pigment.

Removal of the solvent from the combined filtrate and washings (overheating in the later stages of the distillation must be avoided, otherwise darkening and resinification of the pigments ensue) yielded a dark-red residue (2—3 g.) which did not crystallise.

This material was exhaustively extracted with successive portions of boiling benzene (*ca.* 750 c.c. in all). After the combined benzene extracts had been cooled and filtered, the dissolved pigments were chromatographed on a column (15 × 5 cm.) of anhydrous magnesium sulphate (prepared from commercial "anhydrous" material which had been previously heated at 200° for 4 hr. and stored in a desiccator). Development of the chromatogram with dry benzene produced three fractions: (i) a rapidly moving, diffuse, yellow band; (ii) a more slowly moving, vivid red band, and (iii) a mixed zone of dark-brown bands which remained near the top of the column. Continued percolation of dry benzene through the column gave eluates which contained fraction (i) (in 250 c.c.) and fraction (ii) (in 3 l.). Fraction (i) (which consisted of a very small quantity of pale-yellow material) and fraction (iii) were not further investigated. The eluate containing fraction (ii) was concentrated by distillation to 20—30 c.c., and the remaining solvent removed either by gentle heating in a stream of air or *in vacuo* with constant agitation. The residue, after having been washed with cold light petroleum (b. p. 40—60°) until the washings were almost colourless, consisted of a dark-red mass (generally crystalline) of almost pure *purpurogenone* (0·8—1·3 g.), m. p. 306° (decomp.). This material was used, without further purification, for most of the preparative and degradative work described below. For crystallisation, the pigment (50 mg.) was dissolved in boiling acetone (40 c.c.), and the solution was filtered and concentrated to 5 c.c. to give pure purpurogenone (21 mg.).

General Properties of Purpurogenone.—The pigment separated from benzene in dark-red prisms and from acetone (or ethyl methyl ketone) in small, flat, crimson prisms, m. p. 310° (decomp.) [Found: C, 64·5, 64·3, 64·7; H, 4·55, 4·2, 4·2; OMe, 0; *C*-Me, 6·2; active H, 1·3%; *M* (cryoscopic in benzene), 273; *M* (calc. from density of substance, 1·525 g./c.c., and on the assumption of eight molecules per cell of volume 2326 Å^3), 266·9. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·65; 1*C*-Me, 5·8; 3 active H, 1·2%; *M*, 260·2]. It was insoluble in water and light petroleum, sparingly soluble in ether, benzene, acetone, ethanol, chloroform, and glacial acetic acid, and readily soluble, even in the cold, in dioxan. Light absorption (in $CHCl_3$): $\lambda_{max.}$ 252, 306, 387, 498, 528, and 568 mμ; log ε 4·18, 3·73, 3·80, 3·42, 3·47, and 3·27 respectively. Addition of a trace of ferric chloride solution to its solution in ethanol produced an olive-green colour. (Other general properties have been described above.)

Catalytic Hydrogenation of Purpurogenone.—The pigment was dissolved in glacial acetic acid and hydrogenated at atmospheric pressure in presence of either palladised charcoal (5%) or Adams's platinic oxide. In three experiments 0·95, 1·1, and 1·0 mol. of hydrogen were absorbed. During the reduction the intense red colour gave way to pale yellow but rapidly returned when the solution was exposed to air.

Triacetylpurpurogenone.—Two drops of a solution of aqueous 60% perchloric acid (one drop) in acetic anhydride (1 c.c.) were added to a suspension of purpurogenone (0·1 g.) in acetic anhydride (3 c.c.), and the mixture was shaken for 10 min. Complete dissolution soon occurred and the intense red colour changed to pale yellow. The amorphous material, which separated when the solution was poured on crushed ice (75 g.), was collected, washed well with water, and dried (135 mg.). This material was "recrystallised" twice from ethanol to yield *triacetylpurpurogenone* (40 mg.) in pale-yellow granules, m. p. 226°, $[\alpha]_D^{17}$ +105° (*c*, 0·418 in $CHCl_3$) [Found (in a sample dried at 100° *in vacuo* over P_2O_5): C, 62·0; H, 4·6; Ac, 34·0. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7; 3Ac, 33·4%]. Attempts to crystallise this substance from a number of other solvents failed. It chromatographed on a column of acid-washed alumina as a diffused, yellow band. Ultraviolet light absorption (in EtOH): $\lambda_{max.}$ 245, 296 (infl.), and 344—350 (infl.) mμ; log ε 4·26, 3·79, and 3·45 respectively.

Oxidative Degradation of Triacetylpurpurogenone.—Triacetylpurpurogenone (61 mg.) was dissolved in a mixture of acetic anhydride (4 c.c.) and glacial acetic acid (2 c.c.). To this solution, maintained at 70—80°, were gradually added (during ½ hr.) 2·7 c.c. of a solution which had been made by dissolving chromic anhydride (2·5 g.) in water (2 c.c.) and acetic acid (25 c.c.). After having been heated at 95° for 1½ hr., the mixture was cooled and diluted with water (40 c.c.). Extraction with ether (4 × 50 c.c.) gave a yellow extract which was evaporated to to yield a light brown solution (5 c.c.) from which the water and acetic acid were removed by gentle heating *in vacuo*. The brown gum, so obtained, was warmed for 1 hr. on the steam-bath with N-sodium hydroxide (4 c.c.). The solution was cooled, saturated with carbon dioxide, and extracted with ether (20 + 10 c.c.) to remove any phenolic compounds. The aqueous layer was acidified (2N-hydrochloric acid) to pH 2 and extracted with ether (20 + 15 + 10 c.c.).

The solvent was evaporated from the dried (Na_2SO_4) ethereal solution to give a coloured residue (*ca.* 30 mg.). This was dissolved in hot water, and the solution was decolorised with Norite and filtered. From the filtrate there was isolated, by ether-extraction, a partly crystalline material (*ca.* 2 mg.) which gave a pink ferric reaction in water. Paper chromatography revealed the presence in this material of two hydroxy-acids (A and B). The acid, A, gave a reddish-violet spot on paper when sprayed with ferric chloride solution and had $R_F(b)$ 0·62 and $R_F(c)$ 0·02 and was, therefore, almost certainly 3-hydroxybenzene-1 : 2 : 5-tricarboxylic acid. The acid, B, proved identical, in its ferric reaction and in its chromatographic behaviour, with the hydroxy-acid obtained when purpurogenone itself was oxidised with an alkaline solution of hydrogen peroxide (see below).

Degradation of Purpurogenone with 2N-*Sodium Hydroxide.*—A solution of purpurogenone (0·13 g.) in 2N-sodium hydroxide (5 c.c.) was heated, with free access of air, on the steam-bath for 2 hr., the water lost by evaporation being replaced from time to time. To the cooled solution was added phosphoric acid (*d* 1·75; 1 c.c.), and the chocolate-brown precipitate produced was filtered off and washed with water. The combined filtrate and washings were distilled to mimimum volume. After addition of water (5 c.c.) to the residue, distillation was again carried out. This operation was repeated several times. The combined distillates (which had a pungent odour) required 2·41 c.c. of 0·1N-sodium hydroxide (≡ 0·48 mol. of a monobasic acid) for neutralisation to phenolphthalein as external indicator. The neutralised distillates were evaporated to small volume (3—4 c.c.). The solution so obtained (i) reduced a cold, acidified solution of potassium permanganate, (ii) reacted with a warm, neutral solution of mercuric chloride to produce a strong, white turbidity, and (iii) gave a positive result in the chromotropic acid test for formic acid (Feigl, "Qualitative Analysis by Spot Tests," Elsevier, New York, Third English Ed., 1947, p. 397).

The air-dried, chocolate-brown precipitate, mentioned above, was extracted with boiling ether (5 × 50 c.c.), leaving a black, amorphous residue. The combined ethereal solutions were extracted with (i) a saturated solution of sodium hydrogen carbonate (20 + 20 + 10 c.c.) and (ii) 2N-sodium hydroxide (20 + 10 c.c.). The latter extracts, when acidified, yielded a dark-red powder (0·7 mg.) which gave a positive test for a hydroxyquinone when its solution in 2N-sodium hydroxide was warmed with zinc dust. The sodium hydrogen carbonate extracts, when acidified (concentrated hydrochloric acid), gave a copious, dark red, amorphous precipitate which was filtered off (giving filtrate F, see below) and dried (40 mg.). This material was repeatedly extracted with boiling benzene (175 c.c. in all), and the benzene solution of the pigments, after having been left overnight at room temperature, was filtered and poured on a column (8 × 4·5 cm.) of anhydrous magnesium sulphate. The chromatogram, when developed with dry benzene, showed, in order from the top, (i) a brown zone, (ii) a violet band, and (iii) an orange band. The last two bands were eluted from the column with benzene–ether (9 : 1 v/v).

Evaporation of the solvents from the eluate containing the orange band yielded orange-red needles (3—4 mg.), m. p. *ca.* 220° (decomp.) after considerable previous darkening. A further quantity (2 mg.) of this same material was obtained by extraction of filtrate F (see above) with ether, evaporation of the solvent, and crystallisation of the residue from benzene. This material was readily soluble in ether but sparingly soluble in water. Its aqueous solution gave a violet ferric reaction and its solution in 2N-sodium hydroxide gave a positive test for a hydroxyquinone. It dissolved in aqueous solutions of the following reagents to give the colours indicated: (*a*) mineral acid (yellow); (*b*) sodium acetate (orange-red); (*c*) sodium hydrogen carbonate (deep-red); (*d*) sodium hydroxide (intense purple). It dissolved in concentrated sulphuric acid to give an intense crimson colour. The remainder of this pigment was acetylated, a very small quantity of an amorphous, yellow acetate being obtained which, in ethanolic solution, showed maximum absorption in ultraviolet at 255 and 343 mμ [cf. the peak absorption of triacetylflaviolin (Part I, *J.*, 1953, 3302) at 253 and 349 mμ]. There is little doubt that this pigment is a derivative of a 2-hydroxy-1 : 4-naphthaquinone.

The eluate corresponding to the violet band yielded 2 mg. of material (tiny, violet prisms) which, from its properties and colour reactions, appeared to be a hydroxylated quinone or possibly a hydroxylated diquinone.

After the elution of bands (ii) and (iii), the column was extruded and the materials in the brown zone were extracted (Soxhlet) with ether. Evaporation of the solvent yielded an intractable reddish-brown gum (16·5 mg.).

Chromatography of various residues, obtained in the work described in this section, indicated the presence of minute quantities of two other pigments.

Oxidative Degradation of Purpurogenone.—A solution of purpurogenone (0·5 g.) in a mixture

of a 1% solution of sodium hydroxide (80 c.c.) and a 3% solution of hydrogen peroxide (60 c.c.) was kept at room temperature for 3 days, filtered, and extracted with ether (50 c.c.). The aqueous layer was strongly acidified (concentrated hydrochloric acid) and extracted with ether ($60 + 4 \times 50$ c.c.). The combined ethereal extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent yielded a brown gum (*ca.* 120 mg.). Paper chromatography indicated the presence in this gum of only one hydroxy-acid, which gave with ferric chloride a violet "spot" [R_F(b) 0·78; R_F(c) 0·29]. This hydroxy-acid was not identified but it is probably identical with the hydroxy-acid (*B*) produced by chromic acid oxidation of triacetylpurpurogenone.

A solution of the above acid (120 mg.) and of methyl sulphate (1·2 c.c.) in acetone (25 c.c.) was heated under reflux with anhydrous potassium carbonate (1·5 g.) for 19 hr. The mixture was filtered and the acetone removed from the filtrate. The residue, together with the potassium salts, was heated under reflux for 1 hr. with 2N-sodium hydroxide (25 c.c.). After filtration and extraction with ether (20 c.c.)—to remove non-acidic material—the solution was strongly acidified (7·5 c.c. of concentrated hydrochloric acid) and the product collected by ether-extraction to give a partly crystalline, pale-brown material (80 mg.) which had a negative ferric reaction in water.

The solution of this material in 2N-sodium carbonate (3 c.c.) was heated on the steam-bath, and a 4% solution of potassium permanganate (7—8 c.c.) was gradually added. The slight excess of permanganate was destroyed by the addition of a few drops of methanol. The manganese dioxide was filtered off and thoroughly extracted with hot water. The combined filtrate and extracts were strongly acidified (concentrated hydrochloric acid) and extracted with ether (4×40 c.c.). The ethereal extract was washed with water (2 c.c.) and dried (Na_2SO_4). Evaporation of the solvent yielded a pale yellow, semi-crystalline material (30—40 mg.). This recrystallised from hot water (2·5 c.c.) as almost colourless, slender, shining rods which, when dried (14·2 mg.), broke up and became opaque [Found : C, 49·9; H, 3·65; OMe, 12·9%; equiv., 79·8. Calc. for $C_9H_5O_6 \cdot OMe$: C, 50·0; H, 3·35; OMe, 12·9%; equiv. (as a tribasic acid), 80·0], m. p. 253°, re-melting (after the temperature had been raised to 260° and then lowered to 200°) at 252°, R_F(b) 0·76. [A further quantity (8 mg.) of this material was obtained by spontaneous evaporation of the mother-liquor and washings from the first crop of crystals.] A very dilute, aqueous solution of this acid gave a strong yellow ferric reaction. It gave a positive result in the fluorescein reaction for an *o*-phthalic acid. This substance was virtually identical with synthetic 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid (Posternak, *loc. cit.*), R_F(b) 0·76, m. p. 252° unaltered by admixture with the degradation product.

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THE UNIVERSITY, NOTTINGHAM. [*Received, April 7th,* 1955.]

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4 : 4-*Dimethyl Steroids. Part I.* 4 : 4-*Dimethylcalciferol.*

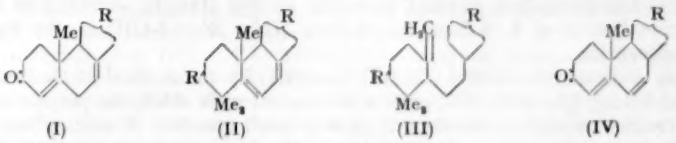
By G. COOLEY, B. ELLIS, and V. PETROW.

[Reprint Order No. 6332.]

Ergosterol has been converted into 4 : 4-dimethylergosterol (II; R′ = β-OH) and thence by irradiation into 4 : 4-dimethylcalciferol (III; R′ = β-OH).

BIOSYNTHESIS of cholesterol in the animal organism appears to proceed from acetate, which is then converted into branched-chain acids such as β-methylcrotonic acid and thence into linked *iso*prenoid precursors which may be of the squalene type (see recent reviews : Liebermann and Teich, *Pharm. Reviews*, 1953, **5**, 285; Ruzicka, *Experientia*, 1953, **9**, 357. Also Popják, *Arch. Biochem. Biophys.*, 1954, **48**, 102; Rabinovitch and Gurin, *J. Amer. Chem. Soc.*, 1954, **76**, 5168; Eidinoff, Rosenfeld, Knoll, Marano, and Hellman, *J. Clin. Invest.*, 1954, **33**, 333; Bloch, Clark, and Isaac, *J. Biol. Chem.*, 1954, **211**, 687). 4 : 4-Dimethyl-steroids may consequently be implicated in steroid biogenesis (Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023; Ruzicka, *loc. cit.*; Clayton and Bloch, *Fed. Proc.*, 1955, **14**, 194) and are therefore worthy of study.

4 : 4-Dimethylcholesterol, required by Woodward, Packett, Barton, Ives, and Kelley (*J. Amer. Chem. Soc.*, **1954**, **76**, 2852) for conversion into lanosterol, was prepared by them by dimethylation of cholestenone followed by reduction of the resulting 4 : 4-dimethyl-

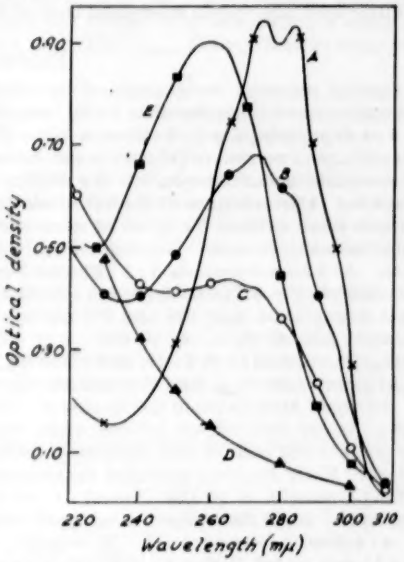


(I) (II) (III) (IV)

(R = $C_{17}H_{33}$)

cholest-5-en-3-one. Extension of the methylation procedure to the ergosterol series is now reported.

Ergosterol was converted into *iso*ergosterone (IV) and ergosterone (I) as described by Johnson, Newbold, and Spring (*J.*, 1954, 1302). Attempts to methylate the ketone (IV)



Ultra-violet absorption spectra of 4 : 4-*dimethylergosterol* ($4{\cdot}0 \times 10^{-5}$ *g./*100 *ml. of ethanol*): *A*, ×, *original*; *B*, ●, *after 2-min. irradiation*; *C*, ○, *after 5-min. irradiation*; *D*, ▲, *after 15-min. irradiation*; (*E*), ■, 4 : 4-*dimethylcalciferol* ($1{\cdot}84 \times 10^{-5}$ *g./*100 *ml. of ethanol*).

in dry *tert.*-butanol with potassium *tert.*-butoxide (3 mols.) and methyl iodide (6 mols.) (Woodward *et al.*, *loc. cit.*; cf. Conia, *Bull. Soc. chim. France*, 1954, 943) yielded mostly unchanged material. Ergosterone (I), in contrast, passed smoothly under these conditions into crystalline 4 : 4-dimethylergosta-5 : 7 : 22-trien-3-one (II; R′ = :O). This structure is supported, not only by the mode of formation, but also by the ultraviolet absorption which closely resembles that of the parent ergosterol. Reduction of the product (II; R′ = :O) with lithium aluminium hydride gave in high yield a homogeneous alcohol, considered to be 4 : 4-dimethylergosterol (II; R′ = β-OH) as its ultraviolet absorption is almost identical with that of the ketone (II; R′ = :O). Its alternative formulation as 4 : 4-dimethyl*epi*ergosterol (II; R′ = α-OH) is rendered unlikely as reduction of similar 4 : 4-dimethyl-3-ketones such as 4 : 4-dimethylcholest-5-en-3-one (Woodward *et al.*, *loc. cit.*), lanostadienone, and euphadienone (Dr. J. F. McGhie, personal communication) with lithium aluminium hydride leads exclusively to 3β-hydroxy-compounds (see also Klyne, "Progress in Stereochemistry," Butterworths Scientific Publ., 1954, Vol. I, p. 74).

Parallel study of the spectral changes undergone by ergosterol and by the alcohol (II; R′ = β-OH) in ethanolic solution on irradiation with ultraviolet light revealed closely similar behaviour (cf. Figure, curves *A* to *D* obtained in small-scale experiments in which

the irradiation was carried out in 5-mm. bore silica tubes with data, for example, in Morton, Heilbron, and Kamm, *J.*, 1927, 2002). Extension of these experiments to the preparative scale led to the isolation as the 3 : 5-dinitrobenzoates of calciferol from ergosterol and of a photochemical transformation product from the alcohol (II; R′ = β-OH) to which we assign the constitution of 4 : 4-dimethylcalciferol (III; R′ = β-OH) on the basis of its ultraviolet absorption.

Oxidation of dimethylcalciferol (III; R′ = β-OH) by the method of Heilbron, Jones, Samant, and Spring (*J.*, 1936, 905) gave a viscous oil with aldehydic properties (Schiff's reagent). Treatment with semicarbazide gave a small quantity of semicarbazone which was probably derived from the $C_{19}H_{32}O$ ketone of Windaus and Thiele (*Annalen*, 1936, **521**, 160), but paucity of material prevented full identification. We also examined the irradiation of the ketone (II; R′ = :O), but obtained the photochemical product only as its semicarbazone, to which we tentatively assign the formulation of 4 : 4-dimethylcalciferone semicarbazone on the basis of its ultraviolet absorption. Cleavage of the semicarbazone by Hershberg's method (*J. Org. Chem.*, 1948, **13**, 542) gave a viscous oil; its ultraviolet absorption resembled that of 4 : 4-dimethylcalciferol (III; R′ = β-OH).

Experimental

Optical rotations were measured in $CHCl_3$ in a 1-dm. tube, unless otherwise stated. Absorption spectra, measured in EtOH, were kindly determined by Mr. M. T. Davies, B.Sc.

4 : 4-*Dimethylergosta*-5 : 7 : 22-*trien*-3-*one* (II; R′ = :O).—Ergosterone (28·5 g.) was added to a solution of potassium (10·9 g.) in *tert.*-butanol (350 ml.; previously distilled over potassium *tert.*-butoxide) under nitrogen, and the mixture stirred and warmed gently until dissolution was complete. After addition of methyl iodide (35 ml.) to the ice-cooled mixture, stirring under nitrogen was continued for 2½ hr. at room temperature, then most of the solvent was removed under reduced pressure. The residue was treated with water, and the product isolated with ether. 4 : 4-*Dimethylergosta*-5 : 7 : 22-*trien*-3-*one* (74%) formed plates (from acetone), m. p. 167—168°, $[\alpha]_D^{24}$ −37° (*c*, 0·75) (Found: C, 85·3; H, 11·0. $C_{30}H_{46}O$ requires C, 85·2; H, 11·0%). Light absorption: $\lambda_{max.}$ 274 and 283 mμ (log ε 4·00, 4·01); infl. 265 and 292 mμ. The *semicarbazone* formed plates, m. p. 259°, $[\alpha]_D^{23}$ −59° (*c*, 1·0) (Found: C, 76·5; H, 10·1; N, 8·8. $C_{31}H_{49}ON_3$ requires C, 77·6; H, 10·3; N, 8·8%), after crystallisation from chloroform–methanol. Light absorption: $\lambda_{max.}$ 228, 273, and 283 mμ (log ε 4·13, 4·09, 4·09); infl. 266 and 292 mμ.

Attempted Methylation of iso*Ergosterone* (IV).—The ketone (1·53 g.) in a solution of potassium (0·6 g.) in *tert.*-butanol was treated, under nitrogen, with methyl iodide (2 ml.). After 2½ hr. the product was isolated and chromatographed in benzene on a column of acid-washed alumina (40 g.). Early fractions provided unchanged material. Later fractions afforded a *substance* (20 mg.), rhombs, m. p. 124° (Found: C, 84·7; H, 11·0%), after crystallisation from acetone–methanol. Light absorption: single peak with $\lambda_{max.}$ 283 mμ.

4 : 4-*Dimethylergosterol* (II; R′ = β-OH).—The ketone (II; R′ = :O) (9·2 g.) in ether (1·4 l.) was added during 90 min. to an ice-cooled suspension of lithium aluminium hydride (6 g.) in ether (500 ml.). The mixture was stirred for 15 min. at room temperature and then heated under reflux for 2 hr. The product, isolated in the usual way and purified from ethanol, gave 4 : 4-*dimethylergosterol* (89%), plates, m. p. 181°, $[\alpha]_D^{25}$ −171·5° (*c*, 0·76) (Found: C, 85·1; H, 11·5. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption: $\lambda_{max.}$ 274 and 283 mμ (log ε 4·00, 4·00); infl. 265 and 292 mμ. The *acetate* formed plates, m. p. 173—174°, $[\alpha]_D^{25}$ −108° (*c*, 0·64) (Found: C, 81·7; H, 10·8. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%), after crystallisation from ethanol. The 3 : 5-*dinitrobenzoate* separated from acetone in plates, m. p. 196—199°, $[\alpha]_D^{23}$ −47° (*c*, 1·11) (Found: C, 71·7; H, 7·9; N, 4·5. $C_{37}H_{50}O_6N_2$ requires C, 71·8; H, 8·1; N, 4·5%). Light absorption: $\lambda_{max.}$ 262, 273, and 282 mμ (log ε 4·18, 4·18, 4·13); infl. 292 mμ (cf. spectrum of ergosteryl 3 : 5-dinitrobenzoate, Huber, Ewing, and Kriger, *J. Amer. Chem. Soc.*, 1945, **67**, 609).

4 : 4-*Dimethylcalciferyl* 3 : 5-*Dinitrobenzoate* [III; R′ = β-$C_6H_3(NO_2)_2$·CO_2].—A suspension of the alcohol (II; R′ = β-OH) (33·5 g.) in ethanol (6·5 l. of 96%) under carbon dioxide was irradiated for 1 hr. with a mercury-vapour lamp. The solution was concentrated under reduced pressure to *ca.* 300 ml.; unchanged material separated and was removed by filtration. Complete removal of solvent gave a yellow resin (17·9 g.), which was treated in pyridine (36 g.) at 0° with 3 : 5-dinitrobenzoyl chloride (15·2 g.), stirred vigorously at room temperature for 20 min., and digested with water. Fractionation of this material from acetone led, after removal of further

quantities of unchanged material, to **4 : 4-*dimethylcalciferyl* 3 : 5-*dinitrobenzoate*** (5·7 g.), pale yellow prisms, m. p. 132—135°, $[\alpha]_D^{23}$ +99° (*c*, 0·84) (Found : C, 71·7; H, 8·0; N, 4·5. $C_{37}H_{50}O_6N_2$ requires C, 71·8; H, 8·1; N, 4·5%). The spectrum showed an absorption increasing steadily in intensity from 280 to 220 mμ with just discernible shoulders at 235 and 260 mμ (cf. calciferyl 3 : 5-dinitrobenzoate, Huber *et al.*, *loc. cit.*).

4 : 4-*Dimethylcalciferol* (III; R′ = β-OH).—The foregoing compound (5 g.) in benzene (10 ml.) was treated with methanolic sodium hydroxide (8·3 ml. of a solution prepared from 700 mg. of sodium and 23 ml. of methanol, diluted with 1·5 ml. of water). The mixture was stirred for 5 min., then filtered, and the sodium 3 : 5-dinitrobenzoate washed once with benzene (2 ml.). The filtrate was washed with water and dried, the solvent removed, and the residue crystallised from methanol. **4 : 4-*Dimethylcalciferol*** (2 g.) formed flat needles, m. p. 122—124°, $[\alpha]_D^{23}$ +85° (*c*, 1·01 in EtOH) (Found : C, 84·4; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption : $\lambda_{max.}$ 260 mμ (log ε 4·32).

The foregoing product (550 mg.) in glacial acetic acid (30 ml.) was treated dropwise with stirring during 1 hr. with chromium trioxide (250 mg.) in 75% acetic acid (1 ml.). After 3 hr. at room temperature the mixture was diluted with water, and the product isolated with ether. The neutral fraction, a yellow viscous oil (530 mg.), was treated with semicarbazide acetate in ethanol, yielding a very small quantity of crystals, m. p. 199°, $\lambda_{max.}$ 231 mμ, intense absorption (cf. Windaus and Thiele, *loc. cit.*).

Irradiation of **4 : 4-*Dimethylergosta*-5 : 7 : 22-*trien*-3-*one*** (II; R′ = :O).—The ketone (II; R′ = :O) (30 g.), suspended in ethanol (6 l. of 96%) and under carbon dioxide, was irradiated for 1 hr. with a mercury-vapour lamp. The solution was concentrated in stages under reduced pressure to *ca.* 45 ml., unchanged material which separated being removed by filtration. Removal of solvent left a yellow brown oil (6·9 g.) which was treated with semicarbazide acetate in ethanol under reflux for 1½ hr. Fractionation of the product from ethanol gave **4 : 4-*dimethylcalciferone semicarbazone*** (420 mg.), pale yellow plates, m. p. 205°, $[\alpha]_D^{20}$ +29° (*c*, 0·72) (Found : C, 76·8; H, 10·1; N, 8·9. $C_{31}H_{49}ON_3$ requires C, 77·6; H, 10·3; N, 8·8%). Light absorption : $\lambda_{max.}$ 235 and 270 mμ (log ε 4·24 and 4·23).

The foregoing compound (400 mg.) in warm glacial acetic acid (4 ml.) was treated with pyruvic acid (110 mg.) and anhydrous sodium acetate (144 mg.) in acetic acid (1 ml.); after 10 min. under reflux the mixture was diluted with water to turbidity, and refluxing continued for a further 50 min. The product, isolated by precipitation with water (12 ml.) and decantation, failed to crystallise : it had $\lambda_{max.}$ 269—270 mμ and formed a yellow dinitrophenylhydrazone.

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*The Constitution of Gum Myrrh. Part II.**

By J. K. N. Jones and J. R. Nunn.

[Reprint Order No. 6379.]

Purified gum myrrh has an equivalent weight of *ca.* 460 and contains D-galactose residues (8), L-arabinose residues (2), and 4-*O*-methyl-D-glucuronic acid residues (7 per repeating unit). On hydrolysis a mixture of reducing sugars and acidic oligosaccharides is produced. Fractionation of the oligosaccharides has yielded two aldobiuronic acids identified as 4-*O*-(4-*O*-methyl-α-D-glucuronosyl)- and 6-*O*-(4-*O*-methyl-β-D-glucuronosyl)-D-galactose in the approximate ratio of 6 : 1. The significance of these results is discussed.

In Part I * the identification of the component sugars of gum myrrh was detailed. The purpose of this communication is to describe attempts to isolate a protein-free polysaccharide and to determine the composition of the acidic disaccharides which are produced when the gum is hydrolysed with dilute acids.

* Part I, Hough, Jones, and Wadman, *J.*, 1952, 796.

Hough, Jones, and Wadman (*loc. cit.*) isolated from gum myrrh a polysaccharide containing approximately 18% of protein. Addition of copper sulphate to an aqueous solution of the alcohol-insoluble gum gave an alcohol-insoluble copper salt which contained protein. We have removed the majority of the protein from the crude polysaccharide by the usual procedures (see Experimental section) and then fractionated it through its copper salt. The results indicate that the fractionation described in the earlier work was probably a separation into carbohydrate-rich and a carbohydrate-poor component and that no real separation of the gum into different polysaccharides had occurred. It was not found possible to eliminate the last traces of protein material and it maybe that it was combined with the polysaccharide.

Hydrolysis of the purified polysaccharide with N-sulphuric acid gave high yields of a mixture of neutral sugars and acidic oligosaccharides. The latter were isolated as their barium salts, which were converted into the ash-free acids and then fractionated on cellulose columns. Two aldobiuronic acids were isolated in the approximate ratio of 1 : 6 and were identified as 6-*O*-(4-*O*-methyl-β-D-glucuronosyl)- and 4-*O*-(4-*O*-methyl-α-D-glucuronosyl)-D-galactose by the standard procedures.

The isolation of these two aldobiuronic acids shows that the polysaccharide component of gum myrrh resembles lemon gum (Connell, Hainsworth, Hirst, and Jones, *J.*, 1950, 1696) and mesquite gum (White, *J. Amer. Chem. Soc.*, 1948, **70**, 367; Smith, *J.*, 1951, 2646) in the main features of its composition. It is becoming increasingly evident that aldobiuronic acids composed of D-glucuronic acid joined to $C_{(4)}$ of a D-galactose residue *via* an α-glycosidic linkage and D-glucuronic acid united through $C_{(6)}$ of a D-galactose residue *via* a β-glycosidic linkage are common components of gums (cf. Charlson, Nunn, and Stephen, *J.*, 1955, 1428). It will be of interest to determine why these two structures are so favoured.

Experimental

Unless otherwise stated, concentration of solutions was carried out at 40°/20 mm., and specific rotations were measured in H_2O. Paper chromatograms were run in (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) (Jones, *J.*, 1953, 1672) or (*b*) butanol–pyridine–water (9 : 2 : 2).

Isolation and Purification of the Polysaccharide.—The gum myrrh was collected by Major P. E. Glover in Central N.E. Africa in January, 1947, and given to us by Sir John L. Simonsen, F.R.S., of the Imperial Institute, London. The gum-resin (550 g.) in the form of yellow or dull red nodules, containing much debris was roughly crushed, and then thoroughly extracted with several changes of hot ethanol, which removed the bulk of the resin. The residue was filtered off, washed with hot ethanol, finely ground, and again extracted with hot ethanol. The residue from this extraction was dissolved in hot water, cooled, and poured into ethanol acidified with hydrochloric acid. The precipitate was filtered off and washed with acetone to give a pale brown powder (189 g.) (Found : sulphated ash, 2·3; N, 3·0%).

To this crude gum acid (18 g.) in water (500 c.c.), which was neutralised with sodium hydroxide, was added a slurry of cadmium hydroxide (cf. Laidlaw and Reid, *J. Sci. Food Agric.*, 1952, **3**, 19) [from cadmium sulphate (10·8 g.) and N-sodium hydroxide (86·5 g.)] at about 60° with very rapid stirring. The precipitate was centrifuged off and from the supernatant liquid more protein was removed by the formation of a water-insoluble chloroform–protein gel (cf. Sevag, Lackman, and Smolens, *J. Biol. Chem.*, 1938, **124**, 425). The method consisted of adding 0·25 vol. of chloroform and 0·1 vol. of butanol (foam prevention) to the carbohydrate–protein solution. The mixture was shaken for 60 min. and then centrifuged; two layers were formed, the lower consisting of a fairly stable chloroform–protein gel. The upper clear, aqueous layer was decanted and the process repeated. After ten such operations a negligible amount of emulsion was obtained, indicating that no more protein was being removed. The clear aqueous solution from the last treatment was passed in turn through columns of IR-120 and IRA-400 resin, and the effluent (pH 2) was poured into ethanol. The precipitate was collected and washed with alcohol and acetone in a centrifuge, to give a white powder (8 g.), $[\alpha]_D^{15}$ +32° ± 1° (*c*, 1·2) [Found, on material dried at 60°/0·2 mm. : equiv. (by titration), 500; corr. for ash, protein, and moisture, 460; sulphated ash, 0·4; N, 1·2; OMe, 6·1%]. Chromatography of the hydrolysate of this material revealed the presence of galactose, arabinose, and 4-*O*-methyl-glucuronic acid.

Quantitative estimation of the non-acidic reducing sugars in this material (cf. Hough, Jones, and Wadman, *loc. cit.*) indicated that galactose and arabinose were present in the approximate molar ratio of 4 : 1.

Attempted Fractionation of the Polysaccharide.—(a) *Action of copper sulphate in neutral solution.* Gum acid (1 g.) (N, 1·2%) was dissolved in water and adjusted to pH 7·0 with aqueous sodium hydroxide. 10% Copper sulphate solution (50 c.c.) was added with rapid stirring, and the precipitate centrifuged. The pale green complex was dissolved in 5% hydrochloric acid (5 c.c.) and poured into methanol. The precipitate was redissolved in water and neutralised with sodium hydroxide. Copper sulphate was added to precipitate the complex, and the pH adjusted to 7·0 with aqueous sodium hydroxide. The polysaccharide was recovered from the copper complex as described above, and washed with methanolic hydrogen chloride, ethanol, and acetone, to give a white powder (fraction A) (0·7 g.). The solution from the first precipitation was acidified and poured into methanol; the resulting polysaccharide was washed (fraction B) (0·1 g.).

Both these fractions were purified by dissolution in water and treatment with IR-120 and IRA-400 resins in turn. They were then precipitated (methanol), washed, and dried (60°/0·1 mm.) as before, and had: fraction A, $[\alpha]_D^{20}$ +31° ± 1°, equiv. 507; fraction B, $[\alpha]_D^{20}$ +17° ± 2°, equiv. 590.

(b) *Action of copper acetate in neutral solution.* Gum acid (1 g.) (N, 1·2%) in water (50 c.c.) was neutralised with aqueous sodium hydroxide. 5% Copper acetate solution was added dropwise with stirring. A precipitate appeared immediately which redissolved, and it required 4 c.c. of copper acetate solution before a permanent precipitate appeared, and a further 6 c.c. for complete precipitation. The precipitate was centrifuged, dissolved in 5% hydrochloric acid, and precipitated in ethanol. The resulting polysaccharide was taken up in water, neutralised with sodium hydroxide to pH 7—8, and again treated with copper acetate solution (5 c.c.). The precipitate was centrifuged and washed, dissolved in 5% hydrochloric acid, and passed through a column of IR-120 resin. The eluate was poured into ethanol, and the precipitated polysaccharide centrifuged, and washed with ethanol and acetone (0·76 g.) (Found: equiv., 460).

The solution from the first precipitation gave a faint positive Molisch test, but when it was poured into methanol only a very small precipitate was recovered.

(c) *Attempted fractionation by alcohol precipitation.* The gum acid (1·0 g.) (N, 1·2%) was dissolved in water (200 c.c.), and alcohol added in increasing quantities, the precipitates being removed by centrifuging. Up to 75% v/v ethanol there was no precipitate. At 80% 0·518 g. (equiv., 515) was precipitated; at 85%, 0·262 g. (equiv., 520); and at 90% a further trace. The material lost (*ca.* 22%) probably remained in solution.

Hydrolysis of the Polysaccharide.—When the crude gum acid was heated in N-sulphuric acid on a water-bath, aldobiuronic acid, R_{Ga} 0·67 (R_{Ga} is relative to galactose) (solvent *a*), appeared after 2 hr. This spot reached maximum intensity at about 12 hr. For the preparation of aldobiuronic acid, the crude gum acid (100 g.), containing about 18% of protein (N × 6·25), in N-sulphuric acid (1 l.) was heated on a water-bath for about 11 hr. The neutralised (barium carbonate) solution was concentrated to *ca.* 100 c.c. and poured into ethanol. The precipitated barium salts were redissolved and reprecipitated. These salts were dissolved in water and, after removal of barium (IR-120 resin), the solution was poured into ethanol. The precipitated material of high molecular weight was removed (centrifuge) and the filtrate evaporated to give a pale yellow amorphous solid (34 g.). Chromatography of this revealed the presence of traces of 4-*O*-methylglucuronic acid, arabinose, and galactose and a high concentration of aldobiuronic acid, together with higher oligosaccharides. On extended irrigation (72 hr.) (solvent *a*) the aldobiuronic acid spot was resolved into two spots, R_{Ga} 0·69 (aldobiuronic acid No. 1) and R_{Ga} 0·59 (aldobiuronic acid No. 2). This mixture (34 g.) was separated on a cellulose column (450 × 55 mm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with butanol–formic acid–water (45 : 1 : 4) to give acid I (11·4 g.), a mixture of the acids (1·2 g.), and acid II (2·0 g.) (all weights as barium salt). A specimen of acid II showed signs of crystallisation after 9 months and had formed large colourless needles after 12 months. Attempted recrystallisation failed, because of its high solubility.

Aldobiuronic Acid I.—The barium salt, after purification by precipitation of an aqueous solution in ethanol, was dried at 60°/0·01 mm. and had $[\alpha]_D^{16}$ +87° ± 4° (*c*, 0·98) (Found: Ba, 15·75; OMe, 6·6, 6·7. Calc. for $C_{24}H_{42}O_{24}Ba$: Ba, 15·7; 2OMe, 7·1%). It (2·7 g.) was methylated with methyl sulphate (15 c.c.) and 40% aqueous sodium hydroxide (45 c.c.). This was followed by a second methylation using methyl sulphate (20 c.c.) and sodium hydroxide (25 g.). Acidification with sulphuric acid and extraction with chloroform yielded a pale yellow

syrup, which was then treated with Purdie's reagents, giving a viscous syrup (2·1 g.). It was distilled (b. p. 120—125° (bath)/0·1 mm., $[\alpha]_D^{24}$ +98° ± 7° (*c*, 0·83 in MeOH) (Found: C, 51·3; H, 7·9; OMe, 50·9. Calc. for $C_{20}H_{36}O_{12}$: C, 51·3; H, 7·7; OMe, 53·0%). This material was hydrolysed by 2N-sulphuric acid at 100° in a sealed tube for 25 hr. The neutralised hydrolysate ($BaCO_3$) was extracted with chloroform in a continuous extractor, to yield a pale yellow syrup, $[\alpha]_D^{18}$ +93° ± 3° (*c*, 0·75); $[\alpha]_D$ +15° ⟶ −22° in 15 hr. (*c*, 1·5 in 5% methanolic hydrogen chloride), R_{MG} 0·87 (solvent *b*), 0·91 (solvent *a*) (R_{MG} relative to tetra-*O*-methylgalactose). The syrup was oxidised with bromine water (4 days) and, after removal of bromine by aeration, the solution was neutralised with silver carbonate and filtered, and silver was precipitated with hydrogen sulphide. The filtrate was evaporated to dryness in a vacuum, and the residue recrystallised from dry ether as large colourless needles, m. p. and mixed m. p. 98—99° with 2 : 3 : 6-tri-*O*-methyl-D-galactofuranolactone. *X*-Ray powder diagrams of this and the authentic specimen were identical.

Isolation of 4-*O*-*Methyl*-D-*glucuronic Acid.*—Barium aldobiuronate I (1 g.) was hydrolysed with 2N-sulphuric acid in a sealed tube at 100° for 12 hr. The neutralised ($BaCO_3$) and filtered solution was poured into ethanol. The precipitated barium salt was centrifuged out, dissolved in water, and then shaken with IR-120 resin until all the barium had been removed. The resin was filtered off, and the solution evaporated, leaving a syrup which was fractionated on a cellulose column with butanol–formic acid–water (45 : 1 : 4) as solvent. Evaporation of the fractions containing uronic acid gave a syrup (0·23 g.), which was refluxed with 1% methanolic hydrogen chloride (10 c.c.) for 6 hr. and then neutralised with silver carbonate. Filtration and evaporation left a syrup which was treated with concentrated ammonia solution (5 c.c.) and left at 0° overnight. Evaporation of this afforded a syrup which rapidly crystallised. Four recrystallisations from absolute ethanol gave large, colourless plates of the amide of methyl 4-*O*-methyl-α-D-glucuronoside, m. p. and mixed m. p. 232°, $[\alpha]_D^{22}$ +143° (*c*, 0·67) (Found: OMe, 28·0. Calc. for $C_8H_{15}O_6N$: OMe, 28·05%).

Aldobiuronic Acid II.—The barium salt, after purification as described for acid I, had $[\alpha]_D^{16}$ +6° ± 4° (*c*, 0·9) (Found: Ba, 15·2; OMe, 6·9, 7·1. Calc. for $C_{26}H_{42}O_{24}Ba$: Ba, 15·7; 2OMe, 7·1%). This salt (0·90 g.), on methylation as above, yielded a pale yellow syrup (0·67 g.), which, on trituration with light petroleum (b. p. 40—50°) and storage at −10°, crystallised in colourless nodules. Recrystallisation from light petroleum gave needles, $[\alpha]_D^{25}$ −44° ± 10° (*c*, 0·6 in $CHCl_3$), m. p. and mixed m. p. 86—88° with the methyl ester of methyl 6-(hexa-*O*-methyl-β-D-glucuronosyl)-β-D-galactoside (Charlson, Nunn, and Stephen, *J.*, 1955, 269). The amide of methyl 4-*O*-methyl-D-glucuronoside was obtained from aldobiuronic acid II in the same manner as for acid I.

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Addition of Free Radicals to Unsaturated Systems. Part XI. The Direction of Radical Addition to 1 : 1 : 3 : 3 : 3-Pentafluoropropene, and the Synthesis of Perfluoro-olefins, -ketones, and -acids.*

By R. N. Haszeldine and B. R. Steele.

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A trifluoromethyl radical attacks the CH group of $CF_3{\cdot}CH{:}CF_2$ to give $(CF_3)_2CH{\cdot}CF_2{\cdot}$, thus showing in a second example that free-radical addition can occur to other than the terminal carbon atom in a system containing a terminal double bond. The photochemical reaction of hydrogen bromide with 1 : 1 : 3 : 3 : 3-pentafluoropropene has also been studied.

New convenient routes to perfluoro-olefins $R_FR_F'C{:}CF_2$ (*e.g.*, perfluoro-*iso*butene), -ketones $R_F{\cdot}CO{\cdot}R'_F$ (*e.g.*, $C_3F_7{\cdot}CO{\cdot}CF_3$), and -acids $R_F{\cdot}CO_2H$ (*e.g.*, $C_2F_5{\cdot}CO_2H$), where R_F and $R_F' = CF_3{\cdot}[CF_2]_n{\cdot}CF_2$ and n is not necessarily the same in R_F and R_F', are described.

The attack of a trifluoromethyl radical or of a bromine atom is on the CF_2 group in the olefins $CF_2{:}CFCl$ and $CF_3{\cdot}CF{:}CF_2$, and on the CH_2 or CH group in $CH_2{:}CF_2$ and $CH_3{\cdot}CH{:}CF_2$ (Parts III, IV, V, VII, and X, *J.*, 1953, 1592, 3559, 3565; *J.*, 1954, 923, 3747). The direction of free-radical addition to 1 : 1 : 3 : 3 : 3-pentafluoropropene (I) is now reported, with trifluoroiodomethane and hydrogen bromide again used as sources of a trifluoromethyl radical and a bromine atom respectively.

Trifluoroiodomethane and 1 : 1 : 3 : 3 : 3-pentafluoropropene react only very slowly at room temperature when exposed to light of wavelength >2200 Å, but considerably faster at 100° where a compound of formula $CF_3{\cdot}[C_3HF_5]{\cdot}I$ is obtained in 80% yield. The adduct could be (II) or (III), but the following evidence shows that only the former is formed, probably exclusively but at least to an extent of 90%.

$CF_3{\cdot}CH{:}CF_2$ (I) $\qquad$ $(CF_3)_2CH{\cdot}CF_2I$ (II) $\qquad$ $CF_3{\cdot}CHI{\cdot}CF_2{\cdot}CF_3$ (III)

Photochemical chlorination of $CF_3{\cdot}[C_3HF_5]{\cdot}I$ gives a dichloride, $C_4F_8Cl_2$, which on treatment with zinc and ethanol gives a high yield (81%) of an olefin C_4F_8. Only $(CF_3)_2CCl{\cdot}CF_2Cl$ derived from (II) could undergo dehalogenation in this way; the compound $CF_3{\cdot}CCl_2{\cdot}CF_2{\cdot}CF_3$ derived from (III) would either not react or would be reduced to compounds such as $CF_3{\cdot}CHCl{\cdot}CF_2{\cdot}CF_3$ and thence $CF_3{\cdot}CH{:}CF{\cdot}CF_3$, and these were not detected. The absence of even a small percentage of the compound $CF_3{\cdot}CCl_2{\cdot}CF_2{\cdot}CF_3$ in the dichloride $C_4F_8Cl_2$ is shown by a comparison of the infrared spectrum of the last compound (C.S. No. 227 †) with that of an authentic sample of 2 : 2-dichloro-octafluorobutane (C.S. 228) prepared by the following route :

$$C_2F_5I + CH_2{:}CF_2 \xrightarrow{h\nu} C_2F_5{\cdot}CH_2{\cdot}CF_2I \xrightarrow{Hg,F_2} C_2F_5{\cdot}CH_2{\cdot}CF_3 \xrightarrow{Cl_2} C_2F_5{\cdot}CCl_2{\cdot}CF_3$$

The direction of addition of a perfluoroalkyl radical to 1 : 1-difluoroethylene is known to be to the CH_2 group (Part VII, *loc. cit.*). 2 : 2-Dichloro-octafluorobutane has also been synthesised by an independent route (G. F. Liptrot, unpublished results).

Final proof of structure for the compound $(CF_3)_2CCl{\cdot}CF_2Cl$ is the identity of its infrared spectrum with that of the 1 : 2-dichloropentafluoro-2-trifluoromethylpropane obtained by reaction of chlorine with perfluoro*iso*butene. The C_4F_8 olefin obtained by dechlorination of $(CF_3)_2CCl{\cdot}CF_2Cl$ was also shown to be perfluoro*iso*butene by comparison of properties and spectrum with a known sample. A further proof of structure is that octafluorobutane $C_2F_5{\cdot}CH_2{\cdot}CF_3$ prepared as above differs in its infrared spectrum from the compound $CF_3{\cdot}[C_3HF_5]{\cdot}H$ obtained by treatment of $CF_3{\cdot}[C_3HF_5]{\cdot}I$ with zinc and acid; by this

* Part X, *J.*, 1954, 3747.

† Spectra thus specified have been deposited with the Society. Photocopies, price 3*s.* 0*d.* each per spectrum, may be obtained on application, quoting the C.S. number, to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

treatment the compound (II) would yield $(CF_3)_2CH{\cdot}CHF_2$ whereas the isomer (III) yields $CF_3{\cdot}CH_2{\cdot}C_2F_5$.

The compound (II) is thus the product from the photochemical chain reaction of trifluoroiodomethane with the olefin (I):

$$CF_3I \xrightarrow{h\nu} CF_3{\cdot} + I{\cdot}$$
$$CF_3{\cdot} + CF_3{\cdot}CH{:}CF_2 \longrightarrow (CF_3)_2CH{\cdot}CF_2{\cdot} \quad \text{Initiation}$$
$$(CF_3)_2CH{\cdot}CF_2{\cdot} + CF_3I \longrightarrow (CF_3)_2CH{\cdot}CF_2I + CF_3{\cdot} \longrightarrow \text{etc.} \quad \text{Chain transfer}$$

Under the conditions used there was no indication of chain propagation to give products $CF_3{\cdot}[CH(CF_3){\cdot}CF_2]_n{\cdot}I$ with $n > 1$.

The ultraviolet spectra shown in the Table on p. 3007 do not enable clear-cut distinction to be made between the structures (II) and (III), but are of interest in revealing the extent of stabilisation of a radical $CH_3{\cdot}CF_2{\cdot}$ by replacement of the hydrogen by alkyl or perfluoroalkyl groups.

On the assumption that the position of the absorption maximum of an iodo-compound RI can be correlated with the radical stability of R· (*J.*, 1953, 1764), replacement of one hydrogen in $CH_3{\cdot}CF_2{\cdot}$ by a CF_3 group to give $CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}$ causes distinct increase in stability, as indicated by the appearance of the maximum for $CF_3{\cdot}CH_2{\cdot}CF_2I$ at longer wavelength (4 mμ shift). Further replacement of hydrogen by a CF_3 group to give $(CF_3)_2CH{\cdot}CF_2{\cdot}$ further increases the stability (shift for the iodo-compound of 6 mμ). Replacement of the hydrogen in $CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}$ by methyl instead of trifluoromethyl produces no shift in the absorption maximum of the iodide, however, and hence, qualitatively, there is little difference in stability between $CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}$ and $CF_3{\cdot}CHMe{\cdot}CF_2{\cdot}$, but an appreciable difference between $CF_3{\cdot}CHMe{\cdot}CF_2{\cdot}$ or $CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}$ and $(CF_3)_2CH{\cdot}CF_2{\cdot}$.

The ultraviolet spectrum of $C_2F_5{\cdot}CH_2{\cdot}CF_2I$ agrees well with that of $CF_3{\cdot}CH_2{\cdot}CF_2I$. Since the spectrum of $CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CF_3$ shows a maximum at 270 mμ, the maximum for the compound (III) would be predicted to be *ca.* 274 mμ and although this is sufficiently different from 277 mμ to favour the isomer (II), the absence of ultraviolet data on compounds containing the system $-CF_2{\cdot}CHI{\cdot}CF_2-$ makes decisive distinction impossible on spectroscopic grounds.

The formation of the compound (II) and its ready conversion into perfluoro*iso*butene opens up a new route to perfluoro-olefins $R_FR_F'C{:}CF_2$ and ketones $R_F{\cdot}CO{\cdot}R_F'$, where R_F and $R_F' = CF_3{\cdot}[CF_2]_n{\cdot}CF_2$ etc., and n need not be the same in R_F and R_F'. The olefins $R_F{\cdot}CH{:}CF_2$ can be obtained by reaction of a perfluoroalkyl iodide R_FI with 1 : 1-difluoroethylene followed by dehydroiodination (Part VII, *loc. cit.*), and their reaction with a perfluoroalkyl iodide $R_F'I$, followed by chlorination and then dechlorination, yields $R_FR_F'C{:}CF_2$, oxidation of which with aqueous potassium permanganate (cf. the ready oxidation of perfluoro*iso*butene; Brice, LaZerte, Hals, and Pearlson, *J. Amer. Chem. Soc.*, 1953, **75**, 2698) produces the ketone. This route to perfluoro-ketones such as $C_2F_5{\cdot}CO{\cdot}C_3F_7$, $(C_3F_7)_2CO$, and $C_6F_{11}{\cdot}CO{\cdot}CF_3$ (C_6F_{11} = perfluoro*cyclo*hexyl) is sometimes preferable to the route *via* perfluoroalkyl Grignard reagents (*J.*, 1952, 3423; 1953, 1748; 1954, 1273) and is illustrated by the synthesis of perfluoropentan-2-one:

$$C_3F_7I + CF_3{\cdot}CH{:}CF_2 \xrightarrow{h\nu} (C_3F_7)(CF_3)CH{\cdot}CF_2I \xrightarrow{Cl_2,\ h\nu} (C_3F_7)(CF_3)CCl{\cdot}CF_2Cl$$
$$(C_3F_7)(CF_3)CCl{\cdot}CF_2Cl \xrightarrow[\text{dioxan}]{Zn} (C_3F_7)(CF_3)C{:}CF_2 \xrightarrow{\text{aq. } KMnO_4} C_3F_7{\cdot}CO{\cdot}CF_3$$

Oxidation of the olefins $CF_3{\cdot}[CF_2]_n{\cdot}CH{:}CF_2$ to the fluoro-acids is particularly easy, since fluorine is present on the olefinic carbon, and provides a better method of converting a perfluoroalkyl iodide into the corresponding acid than does the oxidation of $CF_3{\cdot}[CF_2]_n{\cdot}CH{:}CHI$ outlined earlier (*J.*, 1950, 3037, 2789; 1953, 1548), *e.g.*:

$$C_3F_5I \xrightarrow{CH_2{:}CF_2} C_3F_5{\cdot}CH_2{\cdot}CF_2I \xrightarrow{KOH} C_3F_5{\cdot}CH{:}CF_2 \xrightarrow{\text{Alk. } KMnO_4} C_2F_5{\cdot}CO_2H$$

1 : 1 : 3 : 3 : 3-Pentafluoropropene and hydrogen bromide do not react in the dark, even when heated for a long period. The photochemical reaction of hydrogen bromide with the pentafluoropropene yields hydrogen, unchanged olefin, 1-bromo-1 : 1 : 3 : 3 : 3-penta-

fluoropropane (IV), and 1 : 2-dibromo-1 : 1 : 3 : 3 : 3-pentafluoropropane. The formation of (IV) was unexpected in view of the results of the direction of addition of the trifluoromethyl radical reported above, since if it is formed by a reaction involving radical intermediates, the chain reaction

$$Br\cdot + CF_2{\cdot}CH{:}CF_2 \longrightarrow CF_2{\cdot}\dot{C}H{\cdot}CF_2Br \xrightarrow{HBr} CF_2{\cdot}CH_2{\cdot}CF_2Br\ (IV) + Br\cdot$$

must occur, with radical attack on the CF_2 group rather than on the CH group. This would be the first instance of a bromine atom and a free radical showing different directions of addition to an unsaturated system.

Ultraviolet spectra in light petroleum.

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε		$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
$CH_3{\cdot}CF_2I$	267	340	207	10	$CF_3{\cdot}CHMe{\cdot}CF_2I$ ...	270	330	238	120
$CF_3{\cdot}CH_2{\cdot}CF_2I$ ...	271	290	219	24	$C_2F_5{\cdot}CH_2{\cdot}CF_2I$ ...	271	300	237	70
$(CF_3)_2CH{\cdot}CF_2I$ ...	277	245	232	45	$CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CF_3$	270	288	224	25

Proof of structure (IV) is given by unambiguous synthesis of this substance from 1 : 1 : 1 : 3 : 3-pentafluoro-3-iodopropane (Part VII, *loc. cit.*) by reaction with bromine in the dark ($CF_3{\cdot}CH_2{\cdot}CF_2I \longrightarrow CF_3{\cdot}CH_2{\cdot}CF_2Br$), and infrared spectroscopic examination shows that the compound (IV) (C.S. No. 229) is free from isomers or contaminants.

Addition of hydrogen bromide to the olefin *via* ionic intermediates would give the compound (IV), since the fluoropropene is polarised as $CF_3{\cdot}\overset{\delta-}{C}H{:}\overset{\delta+}{C}F_2$, and at first sight this seems the most probable explanation of the formation of (IV). Separate experiments show that hydrogen bromide does not react with 1 : 1 : 3 : 3 : 3-pentafluoropropene in the dark at the temperatures used for the photochemical experiments, however, even when bromine, which is liberated during the photochemical experiments and might catalyse the ionic reaction of hydrogen bromide, is added; under these conditions only 1 : 2-dibromo-1 : 1 : 3 : 3 : 3-pentafluoropropane is formed by addition to the olefin, and this explains why the dibromide is a product of the photochemical experiments. Moisture, etc., which might act as catalyst for ionic reactions was, as always, eliminated from reaction mixtures used for photochemical experiments.

Although the available experimental evidence suggests that the compound (IV) is formed by free-radical reaction of hydrogen bromide with the olefin, we are reluctant to accept the conclusions that an ionic reaction is not involved and that a bromine atom behaves differently from a trifluoromethyl radical in this instance. Until a similar effect is observed with a different olefin therefore, we prefer to record the experimental observations but not to attempt to interpret them.

Discussion.—The results for the photochemical reaction of trifluoroiodomethane with pentafluoropropene are interpreted on the basis of stability of intermediate free radicals as outlined in earlier Parts, although full discussion is again deferred to a paper summarising and interpreting the results of this series. On this basis the radical $(CF_3)_2CH{\cdot}CF_2{\cdot}$ is more stable than $CF_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$, and this is in accord with the results on 1 : 1-difluoropropene, and with the concept that a tertiary radical $\geqslant C{\cdot}$ is more stable than a secondary radical $>CH{\cdot}$, where the terms tertiary and secondary indicate, not the carbon skeleton, but the number of atoms or groups other than hydrogen which are attached to the carbon atom formally carrying the lone electron (Part V, *loc. cit.*). Stabilisation of $(CF_3)_2CH{\cdot}CF_2{\cdot}$ by hyperconjugation involving ***hydrogen*** on the carbon atom adjacent to the carbon formally carrying the lone electron

is also possible and cannot occur with $CF_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$. Radical attack is thus not on the carbon atom of the CF_2 group, which is the most susceptible to attack on steric grounds, and this provides a second example (cf. 1 : 1-difluoropropene, Part V, *loc. cit.*) that free-radical addition can occur to other than the terminal carbon atom in a system containing a terminal double bond.

It should perhaps be noted that if attack of the bromine atom is on the CF_2 group of pentafluoropropene, it would mean that the secondary radical $CF_3\cdot\dot{C}H\cdot CF_2Br$ is more stable than the tertiary radical $CF_3\cdot CHBr\cdot\dot{C}F_2$, in which hydrogen hyperconjugation is also possible. It was pointed in Part V that although all free radicals so far studied fall into the stability clasification there given, there remains the possibility that by suitable choice of groups R and R′ in a secondary radical RR′CH·, the stability of the secondary radical can be made greater than that of a tertiary radical. The formation of the $CF_3\cdot\dot{C}H\cdot CF_2Br$ radical could thus be ascribed to the greater stabilisation by the CF_2Br group, with hyperconjugation of type $CF_3\cdot\dot{C}H\cdot CF_2Br \longleftrightarrow CF_2{:}CH{:}CF_2\ Br\cdot$, than by analogous hyperconjugation involving the CHBr group in $CF_2\cdot CHBr\cdot\dot{C}F_2$. The double bond in $CF_2{:}CH{:}CF_2$ is not one where such second-order effects are likely to play such a deciding rôle in determining direction of addition, however, and we prefer to leave the issue open.

Experimental

Earlier Parts should be consulted for details of experimental techniques.

1 : 1 : 3 : 3 : 3-*Pentafluoropropene*.—The olefin, prepared in 85% yield by the dehydroiodination of 1 : 1 : 1 : 3 : 3-pentafluoro-3-iodopropane (Part VII, *loc. cit.*), had b. p. −20·7° (Found : *M*, 132. Calc. for C_3HF_5 : *M*, 132), and was spectroscopically pure.

Reaction of Pentafluoropropene with Trifluoroiodomethane.—The olefin (3·80 g., 0·029 mole) and trifluoroiodomethane (8·90 g., 0·045 mole) in a 150-ml. silica tube were exposed to intense ultraviolet radiation (4 days) with the liquid phase shielded. The reaction temperature under these conditions was *ca.* 100°. Distillation *in vacuo* gave unchanged reactants (8·15 g., 64%) (Found : *M*, 174), a mixture of hexafluoroethane (mainly) and fluoroform (0·05 g., *ca.* 5%), identified by means of their infrared spectra, and **1 : 1 : 1 : 3 : 3-*pentafluoro-3-iodo-2-trifluoromethylpropane*** (3·65 g., 80%), b. p. 80°, n_D^{20} 1·347 (Found : C, 14·5; H, 0·3%; *M*, 330. C_4HIF_8 requires C, 14·6; H, 0·3%; *M*, 328).

Reaction of **1 : 1 : 1 : 3 : 3-*Pentafluoro-3-iodo-2-trifluoromethylpropane with Chlorine*.**—The iodo-compound (2·37 g., 0·0072 mole), chlorine (1·02 g., 0·0144 mole), and water (1·0 g.) were exposed to ultraviolet light for 7 days in a silica tube, to give **1 : 2-*dichloro*-1 : 1 : 3 : 3 : 3-*pentafluoro-2-trifluoromethylpropane*** (1·72 g., 88%), b. p. 63° (micro), n_D^{20} 1·306 (Found : C, 18·0%; *M*, 270. $C_4Cl_2F_8$ requires C, 17·7%; *M*, 271).

Preparation of **2 : 2-*Dichloro-octafluorobutane*.**—Chlorine (0·49 g., 0·0069 mole) and **1 : 1 : 1 : 2 : 2 : 4 : 4 : 4-**octafluorobutane (0·388 g., 0·00192 mole), sealed in a silica tube (50 ml.) and irradiated (7 days), gave 2 : 2-dichloro-octafluorobutane (0·465 g., 90%), b. p. 64° (micro), n_D^{20} 1·316 (Found : C, 17·6%; *M*, 271. $C_4Cl_2F_8$ requires C, 17·7%; *M*, 271).

Perfluoroisobutene.—1 : 2-Dichloro-1 : 1 : 3 : 3 : 3-pentafluoro-2-trifluoromethylpropane (0·355 g.) was sealed in a Pyrex tube (20 ml.) with zinc dust (4 g.) and dioxan (4 ml.) and heated to 70° in a rotating furnace (4 hr.). Distillation of the volatile products gave perfluoro*iso*butene (0·234 g., 88%), b. p. 7·0° (Found : C, 23·8%; *M*, 202. Calc. for C_4F_8 : C, 24·0%; *M*, 200). Brice *et al.* (*loc. cit.*) reported b. p. 6·5°. The constitution of the perfluoro*iso*butene was proved by comparison of its infrared spectrum with that of a known sample.

Reaction of Pentafluoroiodoethane with **1 : 1-*Difluoroethylene*.**—The olefin (1·79 g., 0·028 mole), sealed with pentafluoroiodoethane (6·90 g., 0·028 mole) in a 200-ml. silica tube and irradiated for 5 days with the liquid phase shielded, gave unchanged reactants (1·40 g., 16%) and liquid products. These were distilled, to give **1 : 1 : 1 : 2 : 2 : 4 : 4-*heptafluoro-4-iodobutane*** (6·70 g., 91%), b. p. 88° n_D^{20} 1·354 (Found : C, 15·8; H, 0·9. $C_4H_2IF_7$ requires C, 15·5; H, 0·6%), and a fraction (*ca.* 0·4 g.), b. p. 140° (micro), n_D^{20} 1·440, probably $C_3F_5\cdot[CH_2\cdot CF_2]_2\cdot I$.

Treatment of **1 : 1 : 1 : 2 : 2 : 4 : 4-*Heptafluoro-4-iodobutane with Mercurous Fluoride*.**—The iodo-compound (2·0 g.) was heated step-wise to 140° with mercurous fluoride (10 g.) in a Pyrex flask fitted with a reflux condenser. After 4 hr. the volatile products which had passed through the condenser and been collected in a trap cooled in liquid air were distilled to give **1 : 1 : 1 : 2 : 2 : 4 : 4 : 4-*octafluorobutane*** (0·63 g., 48%), b. p. 18° (Found : C, 23·3; H, 1·2%; *M*, 200. $C_4H_2F_8$ requires C, 23·8; H, 1·0%; *M*, 202).

Reaction of **1 : 1 : 1 : 3 : 3-*Pentafluoro-3-iodo-2-trifluoromethylpropane with Zinc and Dilute Acid*.**—Sulphuric acid (20 ml. of 5N) was added to zinc dust (10 g.) and the iodo-compound (1·50 g.), and the mixture was warmed until steady evolution of hydrogen was observed. The volatile products passed through a reflux water condenser, were collected in a trap cooled by liquid oxygen, and then distilled, to give 1 : 1 : 1 : 3 : 3-pentafluoro-2-trifluoromethylpropane

(0·59 g., 63%), b. p. 17° (Found : C, 25·1; H, 1·9. Calc. for $C_4H_2F_8$: C, 23·8; H, 1·0%), shown by infrared spectroscopy to be contaminated by an olefin.

Synthesis of Perfluoropentan-2-one.—**1 : 1 : 3 : 3 : 3**-Pentafluoropropene (3·98 g., 0·030 mole) and heptafluoroiodopropane (10·0 g., 0·032 mole) in a 150-ml. silica tube were exposed to intense ultraviolet light (8 days) at 100° with the liquid phase shielded. The unchanged reactants (37%) were removed *in vacuo*, water (5 ml.) and an excess of chlorine were added to the residual **1 : 1 : 1 : 2 : 2 : 3 : 3 : 5 : 5**-nonafluoro-5-iodo-4-trifluoromethylpentane, and the tube was resealed and shaken. After exposure to ultraviolet light (7 days) the crude reaction product was washed with 5% aqueous sodium hydroxide, then added dropwise (5 hr.) to stirred zinc (20 g.) and refluxing dioxan (100 ml.), in a flask fitted with reflux condenser, at 65—70°. The olefin produced, and the entrained dioxan, were collected in a tube containing water. The lower layer was removed, washed with water, and distilled from phosphoric anhydride, to give **1 : 1 : 3 : 3 : 4 : 4 : 5 : 5 : 5**-*nonafluoro-2-trifluoromethylpentene* (53% overall), b. p. 60° (Found : C, 24·1%; *M*, 298. C_6F_{12} requires C, 24·0%; *M*, 300).

The olefin was heated (120°) and shaken in a 100-ml. autoclave with potassium permanganate (14 g.) and water (60 ml.) for 12 hr., and the excess of permanganate was decomposed by treatment with sulphur dioxide. Ether-extraction followed by removal of the ether and distillation of the residue from an excess of phosphoric anhydride to decompose the ketone hydrate gave a volatile fraction which was combined with a smaller amount of volatile product obtained on opening the autoclave. Distillation *in vacuo* gave carbon dioxide, unchanged perfluorohexene (8%), and perfluoropentan-2-one (52% based on perfluorohexene used), b. p. 30° (Found : C, 22·6%; *M*, 265. C_5OF_{10} requires C, 22·6%; *M*, 266). Haszeldine (*J.*, 1953, 1748) reports b. p. 29·5° for this ketone.

Preparation of Pentafluoropropionic Acid from Pentafluoroiodoethane.—Pentafluoroiodoethane (4·40 g., 0·03 mole) and **1 : 1**-difluoroethylene (1·90 g., 0·03 mole) were heated at 220° in a 20-ml. autoclave for 10 hr. to give **1 : 1 : 1 : 2 : 2 : 4 : 4**-heptafluoro-4-iodobutane (95%) and no unchanged reactants. The crude product was treated with alcoholic potassium hydroxide at 30° (cf. Part VII, *loc. cit.*), and the volatile **1 : 1 : 3 : 3 : 4 : 4 : 4**-heptafluorobutene evolved (72% yield) was sealed in a 35-ml. autoclave with potassium permanganate (8 g.), water (20 ml.), and potassium hydroxide (4 g.). After 6 hours' shaking and heating (80°) there was no unchanged olefin. The aqueous solution was acidified, treated with sulphur dioxide, filtered, and extracted with ether, as described for similar oxidations (*J.*, 1950, 3037, 2789; 1952, 4259). Addition of water and silver carbonate (10% excess) to the ethereal extracts, removal of the ether by evaporation, and freeze-drying of the aqueous solution gave silver pentafluoropropionate (55% yield based on pentafluoroiodoethane); its identity was confirmed by means of its infrared spectrum.

Reaction of **1 : 1 : 3 : 3 : 3**-*Pentafluoropropene with Hydrogen Bromide.*—The olefin (1·23 g., 0·0093 mole) and hydrogen bromide (0·80 g., 0·0099 mole), sealed in a Pyrex tube (50 ml.) and heated at 60° (14 days), underwent no reaction.

The pentafluoropropene (0·767 g., 0·0058 mole), hydrogen bromide (0·49 g., 0·0060 mole), and bromine (1·0 g., 0·0062 mole) were sealed in a 50-ml. Pyrex tube and heated at 60° (6 days) to give unchanged olefin (0·52 g., 68%), unchanged hydrogen bromide (0·485 g., 99%), and **1 : 2**-dibromo-**1 : 1 : 3 : 3 : 3**-pentafluoropropane.

In a typical experiment, **1 : 1 : 3 : 3 : 3**-pentafluoropropene (1·11 g., 0·0084 mole) and hydrogen bromide (0·70 g., 0·0086 mole) in a 50-ml. silica tube were irradiated for 6 days, to give non-condensable products (hydrogen) (*ca.* 0·003 g.), unchanged pentafluoropropene (0·40 g., 36%; identified by infrared spectroscopy), **1**-*bromo*-**1 : 1 : 3 : 3 : 3**-*pentafluoropropane* (*ca.* 0·5 g., 40%), b. p. 44°, n_D^{20} 1·319 (Found : C, 17·1; H, 1·3. $C_3H_2BrF_5$ requires C, 16·9; H, 0·9%), and **1 : 2**-dibromo-**1 : 1 : 3 : 3 : 3**-pentafluoropropane (*ca.* 0·8 g., 50%), b. p. 87°, n_D^{20} 1·379. McBee, Truchan, and Bolt (*J. Amer. Chem. Soc.*, 1948, **70**, 2023) report b. p. 88°, n_D^{25} 1·378, for the last compound.

1-Bromo-**1 : 1 : 3 : 3 : 3**-pentafluoropropane was synthesised by reaction of **1 : 1 : 1 : 3 : 3**-pentafluoro-3-iodopropane (2·8 g., 0·011 mole) with bromine (1·8 g., 0·011 mole) in a Pyrex tube (20 ml.). The liquid phase was irradiated for 5 days, and distillation of the products gave **1**-bromo-**1 : 1 : 3 : 3 : 3**-pentafluoropropane (1·3 g., 55%), b. p. 44° (micro), n_D^{18} 1·320. The infrared spectra of the two specimens of bromopentafluoropropane were identical.

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University Chemical Laboratory, Cambridge. [*Received, May 3rd,* 1955.]

The Reaction Between L-*Cystine-bis-3-phenylhydantoin and Sodium in Liquid Ammonia.*

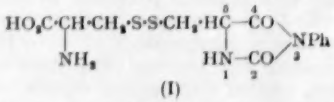
By L. Crombie and K. C. Hooper.

[Reprint Order No. 6388.]

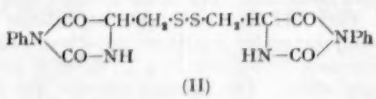
Besides the expected $-S-S-$ and $Ph\cdot CH_2-S-$ cleavage, L-cystine-3-phenylhydantoin (I) * and *S*-benzyl-L-cysteine-3-phenylhydantoin undergo a novel reduction at the 4-position when treated with sodium in liquid ammonia, giving substituted tetrahydro-2-oxoglyoxalines. Complete racemisation ensues: dissolution in liquid ammonia alone is sufficient to cause this. Hydantoins lacking a 3-phenyl substituent are neither reduced nor racemised. The structure of the benzylated reaction product, 4-*S*-benzylthiomethyltetrahydro-2-oxo-1-phenylglyoxaline, is confirmed by desulphurisation to the 4-methyl compound which is synthesised from alanine anilide.

Ultraviolet light absorptions of hydantoins, tetrahydro-2-oxoglyoxalines, and hydantoic acids are recorded in neutral, acid, and alkaline ethanol: there is a remarkable difference between the spectra of tetrahydro-2-oxoglyoxalines and 3-phenylhydantoins. Further, the latter are distinguished from unsubstituted hydantoins by rapid alkaline hydrolysis to 3-phenylhydantoic acids. Ketone stretching vibrations in these compounds agree broadly with the assignments by Randall *et al.* and are useful for identifications.

During an examination of certain peptide degradation products it became necessary to characterise the L-cysteine-3-phenylhydantoin residue * in compounds of type (I) and (II).



(I)



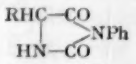
(II)

Oxidation of L-cystine-bis-3-phenylhydantoin (II) by performic acid (Toennies and Homiller, *J. Amer. Chem. Soc.*, 1942, **64**, 3054; Sanger, *Biochem. J.*, 1949, **44**, 126) was expected to yield cysteic acid-3-phenylhydantoin but the latter, in agreement with earlier reports (Andrews and Andrews, *J. Biol. Chem.*, 1933, **102**, 253), was unstable and unsuitable as a reference compound. As an alternative, the bishydantoin (II) was treated with sodium in liquid ammonia, to reduce the disulphide linkage, and then benzylated. However, the product was not *S*-benzyl-L-cysteine-3-phenylhydantoin as expected but a new optically inactive substance $C_{17}H_{18}ON_2S$, m. p. 135°. The same substance was isolated when authentic *S*-benzyl-L-cysteine-3-phenylhydantoin (Shiple and Sherwin, *J. Biol. Chem.*, 1923, **55**, 671) was treated with sodium in liquid ammonia and then rebenzylated. This communication is concerned with the structure and formation of the substance of m. p. 135° and includes spectroscopic data on related compounds.

When *S*-benzyl-L-cysteine-3-phenylhydantoin was merely kept in solution in liquid ammonia for 15 min. and the solvent allowed to evaporate, there was complete racemisation to the DL-compound, m. p. 154°, which was also prepared from *S*-benzyl-DL-cysteine and phenyl *iso*cyanate in the usual way. On the other hand neither *S*-benzyl-L-cysteine-hydantoin itself nor L-cystine-bishydantoin was racemised under these conditions. Ease of racemisation is not associated with the presence of a 3-substituent alone since *S*-benzyl-L-cysteine-3-methylhydantoin retained its optical activity completely after 15 min. in liquid ammonia. The racemisation of hydantoins by sodium hydroxide was discovered by Dakin (*Amer. Chem. J.*, 1910, **44**, 48; cf. Bovarnick and Clarke, *J. Amer. Chem. Soc.*, 1938, **60**, 2426) but there are no records of the use of liquid ammonia for this purpose.

* For convenience, to preserve the amino-acid connexion, this type of nomenclature is retained in this paper. L-Cystine-bis-3-phenylhydantoin (II) can be named systematically di-(1-phenyl-L$_s$-hydantoin-4-ylmethyl) disulphide; L-cystine-3-phenylhydantoin (I) can be named L$_s$-2-amino-2-carboxyethyl 1-phenyl-L$_s$-hydantoin-4-ylmethyl disulphide; and *S*-benzyl-L-cysteine-3-phenylhydantoin can be named L$_s$-5-benzylthiomethyl-1-phenylhydantoin. Ed.

Racemisation undoubtedly involves removal by the base of a proton from $C_{(5)}$, aided by the electron-attracting character of the 4-carbonyl group (equivalent to enolisation postulated by the earlier authors) and the great ease of this process in the 3-phenyl compounds (III) is attributable to increase in the acidity of the 5-hydrogen atom by the electron-attraction of the aryl residue. Reaction of sodium with the bishydantoin (II) in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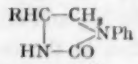
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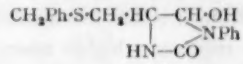

(V)

liquid ammonia is thus probably with already racemised material. The infrared spectrum of the substance, m. p. 135°, indicated that the 4-oxo-group of the original hydantoin had been destroyed but the 2-oxo-vibration was present (see assignments below). The benzylthio-group was then removed by Raney nickel (Mozingo, Wolf, Harris, and Folkers, *ibid.*, 1943, **65**, 1013); the product also showed only the 2-oxo-vibration and its ultraviolet light absorption (cf. Table 2) suggested that a residue of phenylurea type was present. When refluxed with barium hydroxide solution it gave carbonate and an amine, probably a primary amine since it gave a ninhydrin reaction. A tetrahydro-2-oxo-1-phenylglyoxaline system is therefore indicated; the desulphurisation product must be the 4-methyl derivative (IV; R = Me), and the substance, m. p. 135°, must be the 4-benzylthiomethyl derivative (IV; R = CH_2·S·CH_2Ph). These deductions were confirmed by synthesis of the methyl derivative (IV; R = Me).

2-Bromopropionanilide was aminated by Abderhalden and Brockmann's method (*Fermentforschung*, 1928, **10**, 159) and the alanine anilide reduced by lithium aluminium hydride in refluxing tetrahydrofuran to 2-aminopropylaniline. This amine was converted by carbonyl chloride in toluene (Michler and Keller, *Ber.*, 1881, **14**, 2181; Puschin and Mitic, *Annalen*, 1937, **532**, 300) into the glyoxaline (IV; R = Me), identical [mixed m. p. and infrared spectrum (KBr discs)] with our earlier product.

Me·CHBr·CO·NHPh ⟶ Me·CH(NH_2)·CO·NHPh ⟶ Me·CH(NH_2)·CH_2·NHPh ⟶ (IV; R = Me)

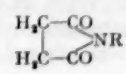
During one reduction of 4-benzylthiomethyl-3-phenylhydantoin (not repeatable) a substance (m. p. 103—104°) was isolated which gave analyses for the hydroxy-compound (V). This represents an intermediate stage in reduction, and the ultraviolet (maximum 237 mμ; ε 13,000 in neutral and alkaline ethanol) and infrared spectra (no 4-oxo-absorption as in hydantoins; 2-oxo-band at 1671 cm.$^{-1}$) agree with this formulation. The tendency of the 4-keto-group to be reduced preferentially was shown by Wilk and Close (*J. Org. Chem.*, 1950, **15**, 1020) who found 3-methyl-5-phenylhydantoin to yield 2 : 3-dihydro-1-methyl-2-oxo-4-phenylglyoxaline on treatment with lithium aluminium hydride.

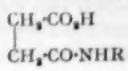
Reduction of L-cysteine-bishydantoin with sodium in liquid ammonia, followed by benzylation, yielded *S*-benzyl-L-cysteine-hydantoin without racemisation or reduction of the 4-oxo-group: the reduction, like the racemisation, is clearly associated with the presence of a 3-phenyl substituent.

The high-intensity ultraviolet absorptions of a number of hydantoins and hydantoic acids are summarised in Table 1. Phenylurea has maximal absorption at 239 mμ (ε 22,000 in neutral or alkaline ethanol) and incorporation into the 2-oxo-1-phenylglyoxaline system causes movement of this to somewhat longer wavelengths (cf. Table 2). When this group is incorporated in the acyclic phenylhydantoic acid system (Table 1) the shift is less pronounced. Pickard and McKay (*Canad. J. Chem.*, 1953, **31**, 896) have recently reported the light absorption of tetrahydro-2-oxo-1-phenlyoxaline, in good agreement with our results (Table 2). In relation to the tetrahydro-2oxo-1-phenylglyoxaline system, the light absorption of the 3-phenylhydantoins is surprising.* The only high-intensity

* We find that a similar spectral effect also occurs in (VI; R = Ph) (end-absorption, $\lambda_{max.}$ 217 mμ; ε 10,500) and (VI; R = *p*-tolyl) ($\lambda_{max.}$ 219 mμ; ε 10,000) as compared with the analogues (VII) (R = Ph: $\lambda_{max.}$ 242 mμ, ε 13,000; and R = *p*-tolyl: $\lambda_{max.}$ 246 mμ, ε 16,000).

(VI)




(VII)

absorption is end-absorption, the maximum lying below 220 mμ. The normal absorption of the phenylurea residue is thus substantially modified by the presence of a 4-oxo-group and some explanation may be found along the following lines (we are grateful to Dr. E. A. Braude for comment on this). Introduction of the 4-oxo-group causes association of unshared electrons of the nitrogen with the $N_{(3)}$–$C_{(4)}$ bond, as is normally the case with amides. Electrons are thus less available at $N_{(3)}$ and excitation to $^{+}N{=}\langle\bigcirc\rangle^{-}$ or related excited states requires a higher energy than in the case of tetrahydro-2-oxo-1-phenylglyoxaline. Consequently the absorption maximum falls to shorter wavelengths. As is expected, the end-absorption of the hydantoins themselves is much weaker than that of the 3-phenyl derivatives.

The ultraviolet absorptions of both hydantoins and 3-phenylhydantoins are influenced by pH (Table 1). In 0·01N-alcoholic potassium hydroxide a maximum appears at 219—224 mμ for hydantoin and 5 : 5-dimethylhydantoin; in neutral or acid ethanol they have

TABLE 1. *Ultraviolet absorption* [a] (λ *in* mμ) *of hydantoins and hydantoic acids.*

Substance	Neutral ethanol	Acid ethanol	0·01N-Ethanolic KOH: Immediate	0·01N-Ethanolic KOH: After 4 hr.	0·01N-Ethanolic KOH: After 24 hr.	Alkaline solution acidified
C; R=R′=R″=H	λ *215; 240*	*215; 240*	*215; 240*	*215; 240*	*215; 240*	*215; 240*
	ε *2800; 165*	*2600; 105*	*3200; 55*	*2700; 60*	*3300; 75*	*2400; 80*
A; R=R′=R″=H	λ *215; 245*	*215; 245*	224	—	224	*216; 245*
	ε *400; 60*	*360; 50*	6200	—	6200	*350; 50*
A; R=R′=Me, R″=H	λ *215; 246*	*215; 246*	219	219	219	*215; 246*
	ε *2100; 150*	*2800; 135*	6650	6300	5900	*1400; 40*
C; R=CH_2Ph·S·CH_2, R′=R″=H	λ *220; 240*	*220; 240*	*220; 240*	*220; 240*	*220; 240*	*220; 240*
	ε *5900; 320*	*5300; 220*	*9400; 760*	*9400; 760*	*9400; 760*	*8400; 710*
A; R=CH_2Ph·S·CH_2, R′=R″=H	λ *215; 245*	*215; 245*	—	238	238	*215; 245*
	ε *4700; 470*	*8250; 1060*	—	7800	8500	*4250; 240*
[*A*; R=·S·CH_2·, R′=R″=H]$_2$	λ *215; 245*	*215; 245*	229—236	234	226	*217; 245*
	ε *6500; 1300*	*5400; 1200*	11,600	17,000	10,800	*4900; 400*
C; R=R′=H, R″=Ph	λ 240	240	240	240	240	240
	ε 19,400	19,000	19,600	19,600	19,600	18,800
A; R=R′=H, R″=Ph	λ *216; 245*	*216; 245*	*216; 245*	242	242	242
	ε *7400; 1050*	*7400; 1050*	*9500; 7030*	19,300	19,300	18,600
C; R=CH_2Ph·S·CH_2, R′=H, R″=Ph [c]	λ 242	242	242	242	242	242
	ε 23,800	22,800	23,400	23,400	23,400	23,400
A; R=CH_2Ph·S·CH_2, R′=H, R″=Ph [d]	λ *215; 245*	*215; 245*	238	238	238	244
	ε *17,500; 1600*	*17,500; 1600*	18,400	18,100	18,100	12,800

[a] Roman numerals indicate maxima; italic numerals indicate end-absorption measured arbitrarily at two wave-lengths. [b] *A*, *B*, *C* denote compounds as below. [c] $\lambda_{max.}$ 239 (ε 22,800 in EtOH) when measured with the Medium Quartz instrument. [d] Substance [*A*; R = ·S·CH_2·, R′ = H, R″ = Ph]$_2$ had λ (infl.) 226 (ε 12,800) in neutral EtOH and $\lambda_{max.}$ 237 (ε 33,000) after 0 and 24 hr. respectively in 0·01N-alkali; substance [*C*; R = ·S·CH_2·, R′ = H, R″ = Ph]$_2$ had $\lambda_{max.}$ 239 (ε 38,000) in EtOH. (All measured on a Medium Quartz instrument.)

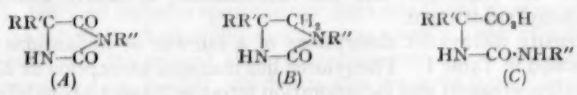


TABLE 2. *Ultraviolet absorption of tetrahydro-2-oxoglyoxalines.*

Compound [a]	$\lambda_{max.}$ (mμ)	ε	Compound [a]	$\lambda_{max.}$ (mμ)	ε
B; R=Me, R′=H, R″=Ph [b]	245	18,400	*B*; R=R′=H, R″=Ph [b, d]	245	19,050
B; " " [c]	246	19,600	*B*; R=R′=H, R″=*p*-tolyl [b, d]	247	19,500

[a] See footnote to Table 1. [b] In EtOH. [c] In ethanolic 0·01N-potassium hydroxide. [d] Pickard and McKay, *Canad. J. Chem.*, 1953, **31**, 896.

only end-absorption. Cystine-bishydantoin and *S*-benzylcysteine-hydantoin, which also have only end-absorption in neutral or acid solutions, develop maxima at 234 and 237 mμ after 4 hours, though the absorption is not constant. When an alkaline solution of any of these four compounds is acidified, these maxima disappear, leaving end-absorption similar to that observed if they are dissolved directly in acid ethanol. Stuckey (*J.*, 1947, 331)

has explained such behaviour by postulating enolisation of the acidic 3-hydrogen atom (cf. Zeif and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2245; Pickett and McLean, *ibid.*, 1939, **61**, 423; Ware, *Chem. Rev.*, 1950, **46**, 403) and our results are consistent with his views: the maxima in alkaline solution are not due to hydrolysis to the corresponding hydantoic

TABLE 3. *Infrared absorption (cm.$^{-1}$) * of hydantoins and tetrahydro-2-oxoglyoxalines.*

Compound †	2-CO	4-CO	Ph$_I$ [d]	Ph$_{II}$ [d]
A; R=R′=R″=H [a]	1697	1776	—	—
A; R=Me, R′=R″=H [a]	1694	1730	—	—
A; R=R″=Me, R′=H [a]	1706	1748	—	—
A; R=$CH_2Ph{\cdot}S{\cdot}CH_2$, R′=R″=H	1686	1739, 1773 [b]	1597	1488
[*A*; R=$\cdot S{\cdot}CH_2\cdot$, R′=R″=H]$_2$	1730 [c]	1754, 1776 [b]	—	—
A; R=R′=H, R″=Ph	1703	1718, 1767 [b]	1595	1497
A; R=Me, R′=H, R″=Ph	1692	1761	1592	1497, 1488
A; R=$CH_2Ph{\cdot}S{\cdot}CH_2$, R′=H, R″=Ph	1692	1724, 1773 [b]	1595	1497, 1488
B; R=Me, R′=H, R″=Ph	1700	—	1595	—
B; R=$CH_2Ph{\cdot}S{\cdot}CH_2$, R′=H, R″=Ph	1682	—	1598	—

* Spectra refer to paraffin mulls; a dash indicates that the vibration was absent.
† See footnote to Table 1.
[a] Randall, Fowler, Fuson, and Dangl, *loc. cit.* [b] It is uncertain which belongs to the 4-oxo-vibration. [c] This lies outside the range given by Randall *et al.* for a 2-oxo-group. [d] Randall *et al.* give 1600 and 1493 cm.$^{-1}$.

acids as these too have merely end-absorption. Maxima given by the sulphur-containing hydantoins in alkali lie at longer wavelengths than would be expected if change involved only the hydantoin ring. The variation of maximal absorption and intensity remains unexplained. Decomposition is doubtless involved as these compounds are unstable to alkali.

The behaviour of 3-phenylhydantoins differs from that of hydantoins lacking this substituent. In neutral or acid ethanol the former show only end-absorption which changes to a high-intensity maximum soon after dissolution in 0·01N-alkali. But on acidification after 24 hours' storage in alkali the maximum remains unchanged in position. The position and intensity of absorption suggest that cleavage to the corresponding phenylhydantoic acid has occurred in alkaline solution. In support of this it was found that 3-phenylhydantoin was completely hydrolysed to 3-phenylhydantoic acid merely by treatment with one equivalent of alkali at 25°. This does not agree with Ware's generalisation (*loc. cit.*, p. 446) that substituted hydantoins are much more stable to hydrolytic agents than are the unsubstituted analogues. Figures in Table 2, and other data obtained during this work, indicate that the *S*-benzyl residue and the disulphide linkage make appreciable contributions to end-absorption in hydantoins, hydantoic acids, and related compounds.

Infrared measurements have accumulated for a number of compounds prepared during this work and some of these are summarised in Table 3. The vibrational assignments are based on investigations of Randall, Fowler, Fuson, and Dangl ("The Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949) who consider that the 2-oxo-stretching vibration in a hydantoin lies at 1670—1710 cm.$^{-1}$ and that of the 4-oxo-group at 1720—1790 cm.$^{-1}$. Our results are broadly interpreted by their assignments, though there are sometimes two carbonyl absorptions in the 4-oxo-region where only one would be expected. As with those of Randall *et al.*, our observations were made on paraffin mulls, to avoid solubility difficulties. Consequently, crystal-lattice effects such as intermolecular hydrogen bonding may be involved.

EXPERIMENTAL

Analyses were carried out in the microanalytical laboratories of Imperial College (Mr. F. H. Oliver). Ultraviolet absorptions were measured in EtOH, unless otherwise stated, by Mrs. I. Boston with a Unicam photoelectric instrument. Those marked * were measured by her with a Hilger Medium Quartz instrument. Some of the infrared data were obtained by Mr. L. Erskin using a Grubb–Parsons double beam spectrometer.

L-*Cystine-bis-3-phenylhydantoin.*—L-Cystine (2·0 g.) was dissolved in N-sodium hydroxide (18 ml.) and water (24 ml.). Phenyl *iso*cyanate (2·0 g.) was added and the cooled suspension shaken until no sharp odour remained. The solution was filtered and acidification precipitated

L-cystine-bisphenylhydantoic acid, m. p. 150°. The crude acid was heated under reflux for 2 hr. with 33% hydrochloric acid (50 ml.) and, on cooling, L-cystine-bis-3-phenylhydantoin crystallised (2·3 g., 62%). After crystallisation (ethanol) it had m. p. 125—127°, $[\alpha]_D^{21}$ −98° (*c*, 0·21 in EtOH) (Found: C, 54·0; H, 4·5. Calc. for $C_{20}H_{18}O_4N_4S_2$: C, 54·5; H, 4·1%). Shiple and Sherwin (*J. Biol. Chem.*, 1923, **55**, 671) give m. p. 117°; Gortner and Hoffman (*ibid.*, 1927, **72**, 433) give 122—123°.

When L-cystine (2·0 g.) was treated with only one mol. of phenyl *iso*cyanate (0·9 g.) as described above, the product, m. p. 123° (1·6 g., 43%), was still essentially L-cystine-bis-3-phenylhydantoin.

Oxidation of L-*Cystine-bis-3-phenylhydantoin with Performic Acid.*—The hydantoin (0·88 g.) was dissolved in formic acid (15 ml.), 30% hydrogen peroxide (1 ml.) added, and the mixture set aside for 1 hr. The solvent was removed *in vacuo* and the oily residue dissolved in ethanol; on addition of water a flocculent mass was precipitated (100 mg.; m. p. 120—128°). Recrystallisation from ethanol–light petroleum (b. p. 60—80°) and concentration of the filtrate gave gluey material, m. p. 75—78°.

Reduction and Benzylation of L-*Cystine-bis-3-phenylhydantoin.*—The hydantoin (0·8 g.) was dissolved in liquid ammonia (200 ml.), and sodium added in small quantities until the blue colour was just permanent. Benzyl chloride (0·8 ml.) was added dropwise, the ammonia evaporated, and the residue treated with 2N-hydrochloric acid (15 ml.). Extraction with ethyl acetate gave *4-benzylthiomethyltetrahydro-2-oxo-1-phenylglyoxaline* (substance *A*) (0·5 g.) which, crystallised from this solvent, had m. p. 135—136°, $[\alpha]_D^{20}$ 0° (*c* 2 in EtOH) [Found: C, 68·1; H, 5·8; N, 9·5; S, 10·0%; *M* (Rast), 329. $C_{17}H_{18}ON_2S$ requires C, 68·4; H, 6·1; N, 9·4; S, 10·7%; *M*, 298].

S-*Benzyl-*L-*cysteine-3-methylhydantoin.*—*S*-Benzylcysteine (11 g.) was dissolved in water (30 ml.) containing sodium hydroxide (2·2 g.). Methyl *iso*cyanate (4·0 g.; prepared according to Boehmer, *Rec. Trav. chim.*, 1936, **55**, 379, in 60% yield) was added, and the suspension shaken. After 15 min. the solution was acidified with hydrochloric acid, and the oily precipitate isolated with chloroform. The oil was refluxed (30 min.) with 20% hydrochloric acid (100 ml.) and sufficient ethanol to effect dissolution. The *product* which separated on cooling had m. p. 115° (8·2 g.), raised on recrystallisation to 117—118°, $[\alpha]_D^{21\cdot5}$ was −35° ± 1° (*c* 1·00 in EtOH) (Found: C, 57·5; H, 5·4. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·6%).

The hydantoin (0·5 g.), dissolved in liquid ammonia (30 ml.), was set aside for 15 min. On evaporation the product had m. p. 117° alone or mixed with the starting material. After one crystallisation from ethanol it had $[\alpha]_D^{21\cdot5}$ −35° ± 1° (*c* 1·00 in EtOH).

S-*Benzyl-*L-*cysteine-3-phenylhydantoin.*—The crude phenylhydantoic acid (m. p. 147°) was prepared from *S*-benzyl-L-cysteine (2·0 g.) and phenyl *iso*cyanate (2·0 g.) in the usual way and heated under reflux for 90 min. with 20% hydrochloric acid (100 ml.) containing sufficient acetone to effect dissolution. The acetone was evaporated and the oily suspension extracted with warm ethyl acetate. Evaporation and crystallisation from ethanol produced *S*-benzyl-L-cysteine-3-phenylhydantoin (2·0 g., 68%), m. p. 120°, $[\alpha]_D^{21}$ −72·8° (*c* 0·88 in EtOH). Shiple and Sherwin (*loc. cit.*) give m. p. 118—119·5°.

Racemisation of S-*Benzyl-*L-*cysteine-3-phenylhydantoin by Liquid Ammonia.*—The L-hydantoin was kept in solution in liquid ammonia for 15 min., and the ammonia then evaporated as speedily as possible, leaving S-*benzyl-*DL-*cysteine-3-phenylhydantoin*, m. p. 154°, $[\alpha]_D^{20}$ 0° (*c* 1 in EtOH) (Found: C, 65·3; H, 5·0; N, 9·5. $C_{17}H_{16}O_2N_2S$ requires C, 65·3; H, 5·2; N, 9·0%).

An authentic specimen was prepared from *S*-benzyl-DL-cysteine (2·0 g.) by the method outlined for the L-isomer. Crystallisation from ethanol gave the DL-hydantoin (2·2 g., 75%), m. p. and mixed m. p. 154°. Under similar conditions L-cystine-bis-3-phenylhydantoin was completely racemised in liquid ammonia but the product was a glass.

Reduction and Benzylation of S-*Benzyl-*L-*cysteine-3-phenylhydantoin.*—The hydantoin (10·0 g.) was dissolved in liquid ammonia (1 l.), reduced, and benzylated as described above. This gave substance A (4·0 g.); m. p. 135°, identical with that mentioned previously.

In one experiment, with hydantoin (1·0 g.), *4-benzylthiomethyltetrahydro-5-hydroxy-2-oxo-1-phenylglyoxaline* (?) (V) (0·4 g.), m p 103—104°, $[\alpha]_D^{21}$ +10° (*c* 1 in EtOH), was isolated (Found: C, 65·1; H, 6·0; N, 8·8. $C_{17}H_{18}O_3N_2S$ requires C, 65·0; H, 5·7; N, 8·9%).

Desulphurisation of 4-Benzylthiomethyltetrahydro-2-oxo-1-phenylglyoxaline.—The substance (2·5 g.) was heated in 90% ethanol (150 ml.) with Raney nickel (40 g) for 4 hr. The suspension was centrifuged, the nickel was washed with acetone, and the combined solutions were evaporated to dryness. The residue of *tetrahydro-4-methyl-2-oxo-1-phenylglyoxaline*, when crystallised from light petroleum (b. p. 40—60°)–ether, had m. p. 102—103° (0·94 g.). It was

also purified by sublimation (98°/10^{-4} mm.) (Found: C, 67·9; H, 7·0; N, 16·0%; *M*, 193. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·9; N, 15·9%; *M*, 176).

This product (200 mg.) was heated under reflux with carbonate-free barium hydroxide (2 g. in 5 ml. of water) for 10 hr. The solution was acidified in a stream of nitrogen, and the evolved carbon dioxide collected as barium carbonate. Filtration from unchanged material, treatment with alkali, and extraction with ether gave the liquid amine which was not further purified. It gave a strong ninhydrin reaction.

DL-*Alanine Anilide.*—α-Bromopropionic acid was converted into its chloride (by thionyl chloride) and anilide (m. p. 99°, from ethanol) in the usual way (96% yield). The anilide (75 g.) was suspended in ammonia (1·5 l.; *d* 0·880), and ethanol (300 ml.) added. Liquid ammonia was cautiously poured in to saturate the mixture and the flask closed with a wired-on stopper and set aside at 20° for 5 days. Evaporation and distillation gave DL-alanine anilide (41 g., 76%), b. p. 133°/0·23 mm., n_D^{19} 1·5710. Abderhalden and Brockmann (*loc. cit.*) give b. p. 190—196°/15—16 mm.

N-2′-*Aminopropylaniline.*—Alanine anilide (6 g.) in dry tetrahydrofuran (50 ml.) was added to a slurry of lithium aluminium hydride (3 g.) in tetrahydrofuran (100 ml.) at such a rate that gentle boiling was maintained. The mixture was heated under reflux for 2 hr. Water was added and the mixture filtered. Evaporation of the filtrate and distillation of the residue gave N-2′-*aminopropylaniline* (3·4 g., 62%), b. p. 106°/0·4 mm., n_D^{20} 1·5638 (Found: N, 18·2. $C_9H_{14}N_2$ requires N, 18·7%). Its orange *picrate* had m. p. 155° (Found: N, 18·1. $C_{15}H_{17}O_7N_5$ requires N, 18·5%).

Synthesis of Tetrahydro-4-methyl-2-oxo-1-phenylglyoxaline.—A solution of *N*-2′-aminopropylaniline (1·9 g.) in toluene (30 ml.) was cooled to 0° and saturated with carbonyl chloride. An oil precipitated which redissolved when warmed. Solvent was removed *in vacuo*. The residual oil solidified when triturated with ether and light petroleum. Filtration gave the crude product (0·4 g., 18%) which was purified by sublimation, then having m. p. 101°, not raised by further purification.

Hydrolysis of 3-Phenylhydantoin.—The hydantoin (0·5 g.) was dissolved in water (50 ml.) containing sodium hydroxide (0·114 g., 1 equiv.) with shaking and set aside for 1 hr. The solution was acidified with hydrochloric acid, and the precipitate (0·47 g.) removed. It had m. p. 196° alone or mixed with phenylhydantoic acid, m. p. 197°.

L-*Cystine-bishydantoin.*—L-Cystine {2·0 g.; $[\alpha]_D^{22}$ −210° (*c* 0·080 in N-HCl)} was suspended in boiling water (10 ml.), and potassium cyanate (1·5 g.) was added. 10% Hydrochloric acid (25 ml.) was added and the mixture heated under reflux (30 min.). L-Cystine-bishydantoin (1·8 g., 74%) separated on cooling; it had no m. p. but decomposed in the range 310—360°; it had $[\alpha]_D^{20}$ −215° (*c* 0·333 in dimethylformamide). A second preparation under similar conditions gave a 69% yield. The product from this, when recrystallised from dimethylformamide, had decomp. 310—360° after shrivelling, $[\alpha]_D^{22}$ −113·3° (*c* 0·300 in dimethylformamide). Hess (*J. Amer. Chem. Soc.*, 1934, **56**, 1421) reports that the substance has no m. p. but decomposes from 310° upwards; he does not record rotation. The above experiments indicate that partial racemisation occurs during the preparation or purification.

When kept in solution in liquid ammonia for 15 min. and then recovered by evaporation of the solvent, both specimens had rotations almost unaltered {$[\alpha]_D^{19}$ −213° (*c* 0·4 in dimethylformamide) and $[\alpha]_D^{20}$ −114° (*c* 0·342% in dimethylformamide) respectively}.

Reduction and Benzylation of L-Cystine-bishydantoin.—The hydantoin (0·29 g.; $[\alpha]_D^{19}$ −213°) was dissolved in liquid ammonia (100 ml.) and sodium added until a blue colour persisted for 10 min. The excess of reagent was just destroyed with ammonium chloride, and benzyl chloride (0·3 g.) added dropwise. After 15 min. the solvent was evaporated and the residue treated with N-hydrochloric acid (15 ml.) and filtered. The filtrate was extracted with chloroform, and the extract evaporated. Crystallisation of the residue yielded *S*-benzyl-L-cysteine-hydantoin (0·35 g., 74%), m. p. 118°, $[\alpha]_D^{20}$ −37° (*c* 0·4 in EtOH) (Found: C, 55·7; H, 5·2. Calc. for $C_{11}H_{12}O_2N_2S$: C, 55·9; H, 5·1%). When the hydantoin of $[\alpha]_D^{20}$ −114° was used, the product (84% yield) had m. p. 118°, $[\alpha]_D^{20}$ −20°.

S-*Benzyl-L-cysteine-hydantoin.*—*S*-Benzyl-L-cysteine ethyl ester hydrochloride (2·6 g.) was dissolved in water (10 ml.) to which a solution of potassium cyanate (0·73 g.) in water (5 ml.) was added. The hydantoic acid was at once precipitated and was heated under reflux with hydrochloric acid until dissolved. Recrystallisation from ethanol gave the hydantoin (1·95 g., 88%), m. p. 118°, $[\alpha]_D^{20}$ −11° (*c* 0·82 in EtOH). On admixture with the specimen having rotation $[\alpha]_D^{20}$ −37°, it had m. p. 117°. A second specimen had m. p. 121°, $[\alpha]_D^{20}$ −12° (*c* 0·209 in EtOH).

S-*Benzyl-DL-cysteine-hydantoin.*—*S*-Benzyl-DL-cysteine (2·11 g.) was treated with potassium

cyanate (0·73 g.) in the usual way, to give the hydantoin (1·7 g., 72%), m. p. 118°, $[\alpha]_D^{20}$ 0°. Admixture with *S*-benzyl-L-cysteine-hydantoin having $[\alpha]_D^{20}$ −11° did not depress the m. p.

Gawron and Glaide (*J. Amer. Chem. Soc.*, 1949, **72**, 3232) give m. p. 129—130° for the L- and 118° for the DL-form of *S*-benzylcysteine-hydantoin (but no rotations). It is clear from the above experiments that some racemisation of the L-form is inevitable during the cyclisation with acid (cf. Dakin, *J. Biol. Chem.*, 1942, **146**, 237) but that products with $[\alpha]_D$ varying from −37° to 0° all have m. p. 118°. No substance of m. p. 129—130° has been encountered.

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Physicochemical Studies on Starches. Part III. The Interaction of Starches and Branched α-1 : 4-Glucosans with Iodine ; and a Valve Microvoltmeter for Differential Potentiometric Titrations.*

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The uptake of iodine by 20 different starches has been studied by differential potentiometric titration, and iodine affinities for these samples are quoted. Contaminating protein alters significantly the apparent iodine affinity of starches. The iodine binding power of amylopectins, glycogens, and other branched α-1 : 4-glucosans has been studied. The differences observed, in conjunction with data for average unit-chain and external-chain lengths, suggest that variations in fine structure (*i.e.*, in degree of multiple branching) exist. In addition, details are given of a valve microvoltmeter developed to extend the scope and accuracy of differential potentiometric iodine titrations.

A QUANTITATIVE estimate of the amount of iodine bound by starch and its components can be obtained by the potentiometric-titration method introduced by Bates, French, and Rundle (*J. Amer. Chem. Soc.*, 1943, **65**, 142). Colorimetric methods developed subsequently (Hassid and McCready, *ibid.*, p. 1154; Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924) are more arbitrary, although useful for comparative measurements. The optical absorption characteristics of the iodine complexes of different amyloses and amylopectins vary (cf. Baldwin, Bear, and Rundle, *J. Amer. Chem. Soc.*, 1944, **66**, 111; Kerr, Cleveland, and Katzbeck, *ibid.*, 1951, **73**, 3916), and the measurements are not absolute or capable of the same accuracy, particularly for amylopectin (cf. Higginbotham and Morrison, *Shirley Inst. Mem.*, 1948, **22**, 141).

Bates and his co-workers (*loc. cit.*) measured the potential between a bright platinum electrode in the starch–iodine–iodide solution and a standard calomel electrode, and thus were able to calculate the equilibrum concentration of free iodine in the mixture. However, the elegant *differential* method of Gilbert and Marriott (*Trans. Faraday Soc.*, 1948, **44**, 84) is much more satisfactory for accurate work at the necessary low free-iodine concentrations. In this technique, the starch–iodine–iodide solution and the blank–iodine–iodide solution are arranged as opposing half-cells connected by a salt bridge; the equilibrium free-iodine concentration in the starch solution can then be found directly, and separate titrations for reagent blanks are not required. As has recently been mentioned (Mould, *Biochem. J.*, 1954, **58**, 593), the scope of the differential technique and the accuracy and reproducibility of results obtained by its use depend on the availability of a null-potential indicator of great zero stability combined with high sensitivity. Such an electronic device, providing high sensitivity (30 mm./mv) and zero stability has already been described (Anderson and Greenwood, *Chem. and Ind.*, 1953, 476). This electrometer gives excellent results for

* Part II, *J.*, 1955, 225.

routine analyses of unfractionated starches, but reliable readings are not possible when the free-iodine concentrations exceed 8×10^{-6}M. The logarithmic decrease in possible sensitivity with increasing free-iodine concentration in both half-cells is an inherent disadvantage of the differential-titration technique. Nevertheless, a ten-fold increase in sensitivity was sought, to permit an accurate study of the iodine-binding power of branched α-1 : 4-glucosans (*e.g.*, the amylopectin component of starch) on which relatively little work has yet been carried out. It appeared possible that such a study could give some details of fine structure.

Mikus, Hixon, and Rundle (*J. Amer. Chem. Soc.*, 1946, **68**, 1115) consider that the low iodine-binding power of branched α-1 : 4-glucosans is inexplicable in terms of hydrogen bonding (cf. Whistler and Hilbert, *ibid.*, 1945, **67**, 1161). They suggested that the large number of branch-points prevents helix formation and decreases the dipolar forces thought to be responsible for complex formation between iodine and the amylose component of starch. [Higginbotham (*Shirley Inst. Mem.*, 1949, **23**, 171) has suggested that, in amylopectin, adsorption of I_2 and I_3^- occurs in addition to complex formation in helices.] The amount of helix formation possible, and hence the iodine uptake, must be related to fine structure. The several model structures proposed for amylopectin [*i.e.*, the "laminated" structure (Haworth, Hirst, and Isherwood, *J.*, 1937, 577; Halsall, Hirst, and Jones, *J.*, 1949, 3200), the "herring-bone" structure (Staudinger and Eilers, *Annalen*, 1937, **527**, 195), and the "ramified" structure (Meyer and Bernfeld, *Helv. Chim. Acta*, 1940, **23**, 857)] all contain different arrangements of the same linear basic chains (Myrbäck and Sillén, *Acta Chem. Scand.*, 1949, **3**, 190), which Peat, Whelan, and Thomas (*J.*, 1952, 4546) have suggested be termed A-, B-, and C-chains. The three models differ, therefore, only in their ratio of A : B chains, *i.e.*, in the *degree of multiple branching*. Similar considerations also apply to other branched α-1 : 4-glucosans. Variations in fine structure must exist to explain the difference in limiting viscosity numbers of the two branched glucosans, amylopectin and glycogen (cf. Greenwood and Robertson, *J.*, 1954, 3769). Any method which can give further indications of differences in fine structure is important.

Experimental

Details of Valve Microvoltmeter.—The few valve millivoltmeters described in recent years (see, *e.g.*, Morton, *Trans. Faraday Soc.*, 1948, **44**, 588; Gray, *Discuss. Faraday Soc.*, 1950, **8**, 331, and personal communication; Scroggie, *Wireless World*, 1952, **14**; Furman, *Analyt. Chem.*, 1954, **26**, 84) were found either to be incapable of modification for our purpose, or, when constructed, had a zero-drift about 100 times greater than required.

Attempts to improve the sensitivity of the original circuit (Anderson and Greenwood, *loc. cit.*) by using miniature valves of high mutual conductance ($g_m = 10$) with 22-v heaters (run from the stabilized high-tension supply) were unsuccessful as the valves would not function under these "under-run" conditions. The desired standard was finally achieved by improving the stability of both high- and low-tension voltage supplies, then amplifying the output by a matched pair of valves functioning as a cathode-coupled amplifier. This design had the advantage of retaining the satisfactory high input impedance and low grid current of the original circuit, and moreover was still simple, depending on fundamental balance of valves and components rather than compensating, and therefore complicating, circuitry. The final circuit is shown in Fig. 1*b*. Very accurate readings can be made up to free-iodine concentrations of 10^{-5}M.

Fig. 1*a* shows how a harmonic-filtered constant-voltage transformer supplies the input voltage to an Ediswan stabilized power unit (Type R1095) and to an accumulator trickle-charger. The latter charges a pile of 12 × 2-v cells (arranged in series/parallel to give 4-v and 6-v outputs) at the same currents as are being taken by the two pairs of valve filaments. A highly insulated switch allows the galvanometer (sensitivity 109 mm./microamp., internal resistance 402 ohm) to be connected either between K_1 and K_2 (so giving the original circuit; sensitivity = 30 mm./mv) or between A_3 and A_4, which gives a sensitivity of 315 mm./mv. In conjunction with the low rate of zero drift attained, this permits potentials of 1 microvolt to be measured. The circuit is extremely stable towards external electrical interferences, since both pairs of valves have been selected *under actual operating conditions* as the best matched pairs obtainable from a large number. The operating conditions of both pairs differ, and are to some extent interdependent; the choice of individual valves to form pairs and of optimum values

for the resistors could only be made by continued " refinements." Wire-wound resistors, matched in pairs to within 1%, are used throughout, and all grid leads are of screened-type coaxial cable. For best results, the electrometer must be adequately protected against vibration, mechanical shock, and local changes in room temperature. The value of R_6 giving the optimum ratio of sensitivity to stability is 330 ohms; decreasing this value gives increased sensitivity, but the circuit may then tend to oscillate, creating instability. Although this can be minimized by inserting " grid-stopper " resistors (47,000 ohms; 0·5 w) inside the grid top-caps of V_3 and V_4, the thermal effects associated with these resistors contributed to zero drift. The introduction of negative feed-back, either by connecting V_2A to V_1G, and V_4A to V_3G, *via* 1 megohm resistors, or by cross-connecting V_4A to V_3Sc and V_2A to V_4Sc, reduced rather than improved stability, and it was shown that zero drift is largely due to fluctuations in the low-tension, and not in the high-tension, supply. Absolute matching of V_3 and V_4 is achieved by connecting both V_3 and V_4 grids to V_1K (with V_1G to V_1K *via* a 2-megohm resistor), and, with P_4 pre-set at its optimum value, P_3 is adjusted so that the galvanometer deflection when connected across A_3/A_4 is zero. After V_4G has been returned to V_2K, P_3 is never altered, and all zeroing adjustments are made by using the " set zero " coarse and fine controls for both A_3/A_4 and K_1/K_2 systems.

FIG. 1(*a*) *and* (*b*).

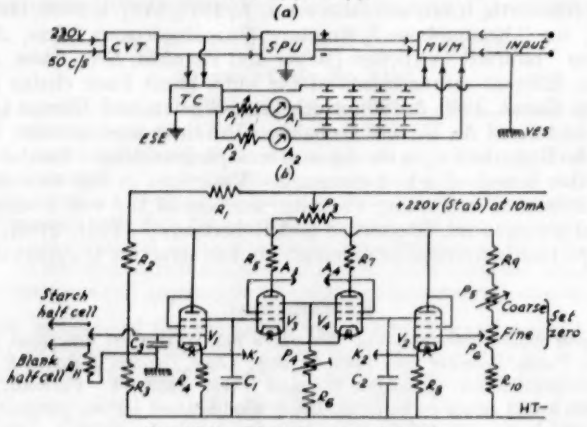

FIG. 1(*a*). *Block diagram of circuit.*

CVT, Constant voltage transformer. SPU, Stabilized power unit. MVM, Microvoltmeter. TC, Trickle-charger. ESE, Electricity supply earth. VES, Virtual earth system. A_1, *Ammeter (set at 0·88 amp.).* A_2, *Ammeter (set at 1·25 amp.).* P_1, 15 Ω/5 *amp.* P_2, 12 Ω/7 *amp.*

FIG. 1(*b*). *Microvoltmeter circuit.*

C_1, C_3, 0·01 μF, *mica.* C_2, 0·1 μF, *mica.* P_3, 500 Ω; P_4, 250 Ω; P_5, 10 *K* (*all* 5 w). P_6, 10Ω/2 w. (*All linear, wire-wound.*)

R_1, 100 *K*; R_2, 68 *K*; R_3, R_{10}, 500 Ω; R_4, R_8, 10 *K*; R_5, R_7, 22 *K*; R_6, 250 Ω; R_9, 65 *K*. (*All* 5 w, *wire-wound.*)

R_{11}, 2*M*, 1 w, *carbon.*

V_1, V_2 = VR 116; V_3, V_4 = VR 65 (SP61); V_1 *and* V_2, *heaters* 4 v *at* 0·88 *amp.*; V_A, 50 v; V_G, 0 v, V_K, 1 v; V_3 *and* V_4, *heaters* 6 v *at* 1·25 *amp.*; V_A, 110 v; V_G, 1 v; V_K, 2·4 v.

The two-way switch shown in the input circuit to V_1 (Fig. 1*b*) must be very highly insulated and must make-before-break so that the grid of V_1 is never on open circuit. A satisfactory switch was made from a thick block of paraffin wax containing pools of mercury, between which contact was made by a tilting copper-wire framework. The inter-electrode resistance is approximately 2 megohms; when the zero-reading of the electrometer is being checked, the grid of V_1 is therefore returned to earth *via* R_{11} so that the operating conditions of V_1 are changed as little as possible.

Details of Titration Cells.—The titration cells (1-l. Pyrex flasks) and salt bridge were similar to Gilbert and Marriott's (*loc. cit.*), except that stirring was automatic and continuous. Additions of iodine were made *via* additional necks in each flask. All four necks were fitted with ground-glass joints, enabling the apparatus to be completely sealed, stirring being made

through Quickfit stirrer glands. [No loss of iodine occurred through volatilization in the time taken for titration (*i.e.*, 40 min.).] The electrodes consisted of platinum foil (2 × 2 cm.). By careful strain-free construction and thorough cleaning, it was possible to obtain a pair of electrodes between which no potential difference existed when placed in the same solution of electrolyte.

Reagents.—All reagents were of "AnalaR" grade, used without further purification.

Preparation of Starch Solutions.—All samples were exhaustively extracted with boiling methanol to remove traces of fat. This is essential. For example, an undefatted sample of commercial rice starch apparently contained 11·8% of amylose, but after being refluxed with methanol (5 treatments; each of 3 hr.) a constant value of 18·5% of amylose was given (7·3% of the original weight of starch was extracted by the methanol). After removal of fat, samples were dried *in vacuo* at 80° for several hours before being weighed by means of a stoppered weighing-stick into a graduated flask. Suitable weights for titration were: starch, 10 mg.; amylopectin and glycogen, 30 mg. Dissolution was achieved by shaking the starch overnight at room temperature with 0·2M-potassium hydroxide (10 ml.) after moistening it with ethanol (2 drops). In certain cases it was necessary to heat the mixture at 95° for 3 min. before shaking. [The effect of pretreatment of whole starch with alkali was investigated as the amylose component degrades in this solvent (Bottle, Gilbert, Greenwood, and Saad, *Chem. and Ind.*, 1953, 541). Ageing at room temperature had no effect, and heating a starch in 0·2M- and 1M-potassium hydroxide for 30 min. at 95° had a negligible effect on the iodine affinity of the sample.] Immediately before addition to the titration half-cell, the alkaline polysaccharide solutions were brought to pH 5·85 by the addition of a predetermined volume of 0·4N-phosphoric acid. A blank solution containing no starch was similarly prepared.

Titration Conditions and Procedure.—Titration conditions were: [iodide], 0·01M; pH, 5·85; temp., 20°. 0·01M-Iodide was chosen so that the addition of 0·01M-iodine–potassium iodide did not alter the iodide concentration in the half-cells during a titration, and thus corrections such as applied by Mould (*loc. cit.*) were avoided. The electrolyte solution (2 l.) contained 0·1M-potassium iodide (210 ml.) and M/15-phosphate buffer (15 ml.; pH, 5·85). This solution (800 ml.) was placed in each half-cell, and stirred for 30 min. in the thermostat to allow for temperature equilibrium. The neutralized polysaccharide and blank solutions were then added to their respective half-cells and the standard flasks carefully rinsed, giving a total volume of 840 ml. (*i.e.*, [iodide], 0·01M). With careful preparation of all solutions, and with temperature equilibration, no significant off-balance potentials existed at the start of titrations, and the "depolarizing" procedure described by Gilbert and Hybart (see Gilbert, Greenwood, and Hybart, *J.*, 1954, 4454) was not necessary. Points on the titration curve were obtained by adding small increments of 0·01M-iodine–potassium iodide by means of an "Agla" micrometer syringe to the solution cell, then adding the same iodine solution to the control until the concentration of free iodine in each was identical, after 2—5 min. (or longer for branched glucosans) had been allowed for equilibration. The difference between the volume of iodine added to the solution cell and that added to the control gave the amount of iodine bound by the starch, the iodide concentrations in each cell being identical. The total free iodine in the starch solution (*i.e.*, $I_2 + I_3^-$) was plotted against mg. of iodine bound per 100 mg. of polysaccharide.

Reproducibility of Technique.—Results were independent of the time taken to complete a titration curve (provided true equilibration had been achieved at each free iodine concentration), and also of the sample weight. The reproducibility is within ±2% of the iodine affinity for an unfractionated starch (*i.e.*, for a starch having an iodine affinity of 5·0%, the results of 6 determinations lay between 4·9 and 5·1%).

As described by Gilbert and Hybart (*loc. cit.*), addition of excess of thiosulphate enabled the titration curve for any starch sample to be repeated. When the titration was repeated at 24- or 48-hr. intervals for 14 days, the starch solution being left in contact with iodine throughout, the observed changes in iodine affinity could be attributed to retrogradation of the amylose component. For waxy maize starch, the titration curve was unaltered after the sample had been in contact with iodine for 17 days. Similarly, for rabbit-liver glycogen, the curve was unaltered after contact with iodine for 21 and 31 days.

Results and Discussion

Fig. 2 shows some typical titration curves for starch samples obtained by plotting the amount of bound iodine against the total free-iodine concentration. Each starch was characterized by its "iodine affinity," which is a measure of the preferential uptake of

iodine by the linear amylose component. At the free-iodine concentration saturating the amylose, the amount of iodine bound by the amylopectin is not negligible (see Anderson and Greenwood, *Chem. and Ind.*, 1954, 642, and below). An estimate of the amount of iodine bound by the amylose component was therefore obtained by extrapolating the linear portion of the titration curve to zero free-iodine concentration. All iodine affinities quoted here were calculated on this basis. The percentage of amylose in a starch can be calculated from this value when the corresponding value for pure amylose is known (Bates and his co-workers, *loc. cit.*). However, as previously mentioned (Greenwood and Robertson, *loc. cit.*), the only accurate method of doing this involves experimental determination of the maximum iodine-binding power of the *pure* amylose component of the starch under examination. Hence, when it is not desired to fractionate any starch exhaustively, it is more satisfactory to quote its iodine affinity, rather than an arbitrary percentage of amylose

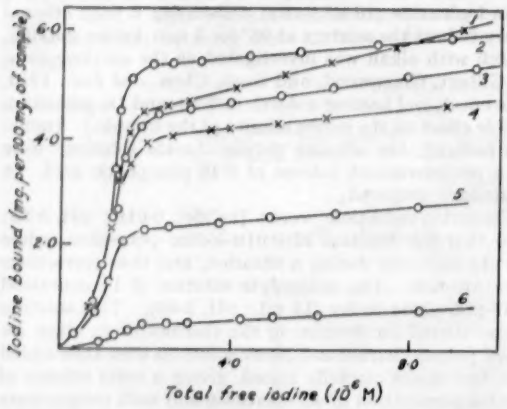

FIG. 2. *Typical iodine-titration curves for starches.*

1, *Potato (Golden Wonder).* 2, Iris germanica. 3, *Barley II.* 4, Hevea brasiliensis. 5, *Parsnip.* 6, *Waxy maize.*

(cf. Schoch in Radley, "Starch and its Derivatives," Chapman and Hall, London, 1953, Vol. 1, p. 123). For comparison with other workers' results, however, percentages of amylose have been calculated, using 19·2% of bound iodine as the maximum iodine-binding power of pure amylose under our experimental conditions (Greenwood and Robertson, *loc. cit.*).

Table 1 summarizes the results for starch samples. It is of interest that starches from different varieties of the same botanical source may show variation in the apparent percentage of amylose; this is in agreement with Doremur, Creshaw, and Thurber's results (*Cereal Chem.*, 1951, **28**, 308). The slope of the linear portion of the titration curve for all the potato starches studied was considerably greater than for other starches.

Contaminants affect the amount of iodine bound by a starch. Interference by fatty acids is well known (cf. Mikus, Hixon, and Rundle, *loc. cit.*). In addition, protein has now been found to have considerable effect (see Table 2), and its presence causes distortion of the titration curve. For oat starch, the effect is to increase the apparent binding power; the protein removes free iodine from solution, and estimates of the true affinity are best obtained by *not* correcting for the percentage of protein present. However, for rubber seed and pea starches, and for synthetic mixtures of protein with potato starch, the protein apparently suppresses starch–iodine complex formation. Interference by protein has also been found during the study of protozoal starches (unpublished observations). It is therefore essential to remove contaminating protein before titrations are attempted.

As briefly reported (Anderson and Greenwood, *loc. cit.*), the difference in iodine-binding power of normal amylopectins and glycogens is sufficiently large to characterize these two structure types. The iodine-binding power of these materials must be fundamentally related to differences in the average length of unit chain, degree of multiple branching, and external-chain length. For a group of polysaccharides having a similar degree of

TABLE 1. *The iodine-binding power of starches.*

Source of starch *	No. of detns.	Iodine affinity †	Amylose (%) ‡	Slope of linear portion of curve §
Arrowroot	4	3·94	20·5	0·13
Banana	3	3·23	16·8	0·10
Barley I	2	4·22	22·0	0·12
Barley II	4	4·22	22·0	0·12
Hevea brasiliensis seed	3	3·86	20·0	0·10
Iris germanica	3	5·18	27·0	0·09
Maize	3	4·61	24·0	0·11
Oat I	2	5·00	26·0	0·13
Oat II	7	5·00	26·0	0·13
Parsnip	4	2·13	11·1	0·08
Pearl manioc	2	3·02	15·7	0·07
Potato I	7	3·94	20·4	0·28
Potato II	4	4·03	21·0	0·24
Potato III	2	4·03	21·0	0·23
Rice	6	3·55	18·5	0·09
Sago	4	5·00	26·0	0·08
Sweet potato	2	3·42	17·8	0·27
Tapioca	4	3·21	16·7	0·07
Waxy maize	5	0·27	1·4	0·06
Wheat	6	4·80	25·0	0·05

* Origin of samples as in Part II of this series (*loc. cit.*), except for *Hevea brasiliensis* seed (Greenwood and Robertson, *loc. cit.*).

† Expressed as mg. of iodine bound per 100 mg. of starch.

‡ Calc. as iodine affinity ÷ 19·2.

§ Expressed as % of iodine bound per total free-iodine concn. × 10^6(M) [range of total free iodine (2—10) × 10^{-6}M].

TABLE 2. *The effect of contaminating protein on the iodine-binding power of starches.*

Starch sample	Protein (%) *	No. of detns.	Iodine affinity † Sample wt. uncorr.	Iodine affinity † Sample wt. corr. for protein
Hevea brasiliensis seed A [a]	0·31	3	—	3·86
Hevea brasiliensis seed B	2·56	2	—	3·01
Oat II (*a*) [b]	0·19	6	5·00	5·00
,, II (*b*)	0·45	3	5·44	5·48
,, II (*c*)	2·94	3	5·97	6·14
,, II (*d*)	22·7	3	5·27	6·80
,, II (*e*)	45·6	2	4·78	8·80
Pea (proteinaceous) [c]	37·5	2	—	9·20
Pea (chloral hydrate extracted)	4·93	1	—	15·1
Potato I	0	7	—	3·94
,, + edestin	2·0	1	—	3·78
,, ,,	10·0	1	—	3·05
,, + egg albumin	2·5	1	—	3·66
,, ,,	16·5	1	—	2·93
,, + tyrosine	11·0	1	—	3·45

* % of N, × 6·25.

† Expressed as mg. of iodine bound per 100 mg. of starch.

[a] Greenwood and Robertson, *loc. cit.* [b] Anderson and Greenwood, *J. Sci. Food Agric.*, in the press. [c] Sample kindly provided by Dr. E. J. Bourne; see *Nature*, 1948, **161**, 206.

branching, it is also probable that variations in the amount of iodine bound are related to the length of *external chain* available for helix formation.

Titrations of different amylopectin samples have always shown evidence of preferential uptake of iodine by linear material. To compare iodine-binding powers, therefore, such preferential uptake has been corrected for by extrapolating the titration curve to zero free-iodine concentration, with this extrapolated point being taken as the origin for the iodine-binding curve. [This preferential uptake was presumably due to contaminating amylose; this is extremely difficult to remove (cf. Gilbert, Greenwood, and Hybart, *loc. cit.*), and the presence of some long branches in the amylopectin cannot be entirely excluded (cf. Swanson, *J. Biol. Chem.*, 1948, **172**, 825).] In all the glycogen samples so far examined there was no evidence of preferential uptake.

Fig. 3 and Table 3 show the results for some amylopectins and glycogens. In the range

of concentrations employed, the amount of iodine bound is directly proportional, within experimental error, to the total free-iodine concentration. This would be expected if the iodine is bound as a co-linear core of iodine and tri-iodide molecules arranged end-to-end in the available helices. One iodine molecule can be accommodated in a helix of about six glucose units (Baldwin, Bear, and Rundle, *J. Amer. Chem. Soc.*, **1944**, **66**, 111). Since the length of external chain available for helix formation is only 14—18 glucose units (*i.e.*, about three helices) for amylopectins, and 8—11 glucose residues (*i.e.*, 1—2 helices) for glycogen (cf. Manners, *loc. cit.*), the amount of iodine-binding possible is small.

Higginbotham (*loc. cit.*) has suggested that *adsorption* of iodine molecules (or tri-iodide ions) may also occur. However, at the low iodine concentrations used here, adsorption effects would be small, and are indeed unlikely to occur in view of the negligible effect on the titration curves of increased polysaccharide concentrations.

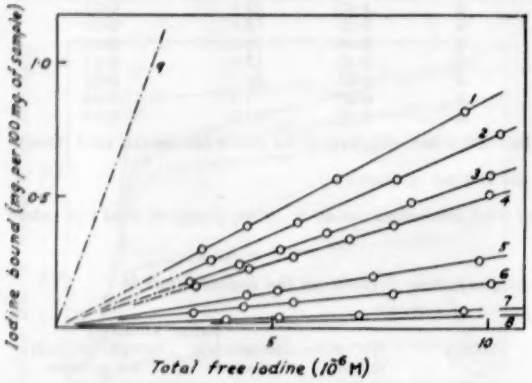

FIG. 3. *The iodine-binding power of branched* α-1 : 4-*glucosans.*

1, *Barley II amylopectin.* 2, Hevea brasiliensis *seed amylopectin.* 3, *Waxy maize starch.* 4, *Oat I amylopectin.* 5, *Glycogen (chain-length* 18 *glucose units).* 6, *Zea mays polysaccharides.* 7, Tetrahymena pyriformis *polysaccharide.* 8, *Rabbit-liver glycogen.* 9, *Wrinkled-pea amylopectin.*

Fig. 3 shows that waxy maize starch behaves as a typical amylopectin, and the polysaccharide from the ciliate *Tetrahymena pyriformis* (Manners and Ryley, *Biochem. J.*, 1952, **52**, 480) as a glycogen. Molecular weight must be of minor importance. For example,

TABLE 3. *The iodine-binding power of branched* α-1 : 4-*glucosans.*

Sample	Linear material (%)	Slope of titration curve *	Av. length of unit chain	Length of external chain †
Barley II amylopectin	2·6	0·090	23 [a]	16 [g]
Hevea brasiliensis amylopectin	0·8	0·074	23 [a]	—
Oat I amylopectin	3·2	0·052	20·3 [a]	—
Ascaris lumbricoides glycogen	—	0·009	12 [b]	—
Rabbit-liver glycogen	—	0·006	13 [b]	8 [b]
Tetrahymena pyriformis polysaccharide	—	0·007	13 [b]	8—9 [b]
Waxy maize starch	1·4	0·060	20 [a]	15—16 [b]
Rabbit-liver glycogen	—	0·028	18 [c]	12
Wrinkled-pea amylopectin	3·4	0·485	36 [d]	—
Zea mays polysaccharide (insoluble)	0·26	0·019	12 [e]	8
" " "	0·6	0·017	13 [f]	9
" " (soluble)	0·6	0·007	11	7

* Expressed as for Table 2. † No. of glucose units removed on β-amylolysis +2·5.

[a] Part II, *loc. cit.*; [b] Manners, *Ann. Reports*, 1953, **50**, 288; [c] Haworth, Hirst, and Isherwood, *J.*, 1937, 377; [d] Potter, Silveira, McCready, and Owens, *J. Amer. Chem. Soc.*, 1953, **75**, 1335; [e] Dvonch and Whistler, *J. Biol. Chem.*, 1949, **181**, 889; [f] Dr. W. J. Whelan, personal communication; [g] Aspinall, Hirst, and McArthur, *J.*, 1955, in the press.

the amylopectin from rubber-seed starch (D.P. 6000) binds about ten times more iodine than rabbit-liver glycogen (D.P. 30,000). (For values of D.P., see Greenwood and Robertson, *loc. cit.*)

It was possible to test the hypothesis that fine structure governed iodine-uptake when samples of " abnormal " branched α-1 : 4-glucosans became available. Samples of the

water-soluble polysaccharides from sweet corn (*Zea mays*) were kindly placed at our disposal by Drs. R. L. Whistler and W. J. Whelan. The exact structural nature of these polysaccharides has been in dispute (cf. Morris and Morris, *J. Biol. Chem.*, 1939, **130**, 535; Hassid and McCready, *J. Amer. Chem Soc.*, 1941, **63**, 1132; Sumner and Summers, *Arch. Biochem.*, 1944, **4**, 7; Cameron, *Genetics*, 1947, **32**, 459; Dvonch and Whistler, *J. Biol. Chem.*, *loc. cit.*). Whilst these materials have an average length of unit chain of 12—13 and 10—11 glucose residues respectively (*idem*, *loc. cit.*; Whelan, personal communication), the iodine-uptake was three to four times greater than that for a glycogen of corresponding average chain length (see Table 3), although the molecular weights were of the same order (Greenwood, unpublished work). It is, therefore, suggested that these polysaccharides have a degree of multiple branching *intermediate* between those of glycogen and amylopectin, and are therefore neither in the one class nor the other. [It is of interest that Wolff, Watson, and Rist (*J. Amer. Chem. Soc.*, 1953, **75**, 4897) reached a similar conclusion from a study of the tricarbanilates of polyglucosans with different linkages.]

An abnormal rabbit-liver glycogen [shown by Haworth, Hirst, and Isherwood (*loc. cit.*) from methylation studies to have an average unit chain of 18 glucose residues] bound about five times more iodine than a normal glycogen and appeared to behave more as an amylopectin-type structure. Without additional information, it is not possible to say whether this is due to the increased average length of the external chains (*i.e.*, 12 residues) or to a variation in the degree of branching. [The abnormal character of this glycogen has been confirmed by Professor F. Smith (personal communication), who found it to possess an abnormal precipitin reaction with concanavalin-A.]

The amylopectin from wrinkled-pea starch (*var.* Perfection) has been shown to possess abnormal iodine-binding power, and an average unit chain of 36 glucose residues (Potter, Silveira, McCready, and Owens, *loc. cit.*). These authors deduced from spot tests that no amylose was present. A sample of this material, kindly provided by Dr. R. M. McCready, gave an abnormal titration curve indicating the presence of some linear material. The iodine-binding power was about six times greater than that for a normal amylopectin (Table 3).

Although data regarding the average external chain length of the amylopectins studied are not complete, the results quoted in Table 3 suggest that small variations may exist in the degree of multiple branching of this group of polysaccharides. Additional evidence might be obtained from a study of the appropriate limit dextrins (cf. Foster and Smith, *Iowa State Coll. J. Sci.*, 1953, **27**, 467), and experiments on these lines are in progress. Similar effects have been found from a study of a large number of glycogen samples (Greenwood and Manners, unpublished work).

Hence, potentiometric determinations of the amount of iodine bound by branched α-1 : 4-glucosans, in conjunction with estimations of chain length, should enable an estimate of the degree of multiple branching to be obtained if the method can be confirmed by enzymic degradative experiments (Peat and his co-workers, *loc. cit.*; Hirst and Manners, *Chem. and Ind.*, 1954, 224). Such experiments are now in progress in these laboratories.

It is of interest that, for the samples studied, the slope of the linear portion of the titration curve for a whole starch is greater than that for the corresponding isolated amylopectin. This implies that sub-fractionation has occurred, and emphasizes the importance of study of all supernatant and precipitated materials obtained during fractionation (cf. Greenwood and Robertson, *loc. cit.*).

The authors thank Professor E. L. Hirst, F.R.S., for valuable advice and criticism. They are indebted to Drs. E. J. Bourne, D. J. Manners, W. J. Whelan, and R. L. Whistler for kindly providing samples, and to Messrs. D. A. Blackadder and D. R. Kennedy for carrying out some of the titrations. Helpful discussions with Mr. C. H. C. Mathews regarding electrometers are also acknowledged.

Department of Chemistry, University of Edinburgh. [*Received, March 1st*, 1955.]

An Ion-exchange Method for the Separation of Partially Methylated Sugars, and its Application in an Improved Preparation of 2-O-*Methyl*-D-*glucose.*

By M. V. Lock and G. N. Richards.

[Reprint Order No. 6274.]

Certain mixtures of carbohydrates may be resolved by preferential adsorption on the borate form of a strongly basic ion-exchange resin. Monosaccharides having positions **1**, **2**, and **4** unsubstituted can be separated on the preparative scale from those having substituents in any of these positions, and similarly, glycosides having a *cis*-glycol grouping can be separated from those not containing such a group. The value of the method is illustrated in a simplified preparation of 2-*O*-methyl-D-glucose.

The separation of partially methylated derivatives is a very common problem in carbohydrate chemistry, the difficulties being particularly acute when derivatives of a similar degree of substitution are involved. On the micro-scale, however, successful separations of this type have been achieved in certain cases by taking advantage of the formation of ionised complexes of the sugar derivatives with boric acid or alkali borates (*e.g.*, Foster and Stacey, *J. Appl. Chem.*, 1953, **3**, 19; Bell and Northcote, *Chem. and Ind.*, 1954, 1328; Barker and Smith, *ibid.*, p. 19) and it was possible by this method to separate mixtures which could not otherwise be resolved. In spite of the success of these analytical procedures, the preparative aspect of the problem appears to have been neglected.

The procedure described below utilises the borate form of the strongly basic ion-exchange resin Amberlite IRA-400, which forms strongly adsorbed complexes with certain partially methylated sugars while having little effect on others. This adsorption is clearly analogous to that originally noted for glycerol on similar resins (Zager and Doody, *Ind. Eng. Chem.*, 1951, **43**, 1070) and later utilised by Khym and Zill (*J. Amer. Chem. Soc.*, 1952, **74**, 2090) and Zill, Khym, and Cheniae (*ibid.*, 1953, **75**, 1339) in the chromatographic analysis of monosaccharide and disaccharide mixtures. The present method has been successfully used for separations of several mixtures of partially methylated sugars on the preparative scale by the batchwise use of the resin. The batch technique is simpler in operation than chromatographic procedures, and, by the use of more concentrated solutions, may be applied to much larger amounts of material.

Böeseken (*Adv. Carbohydrate Chem.*, 1949, **4**, 189) has emphasised that the most stable borate complexes of this type are formed in the 1 : 2-position with the furanose form of the sugar and accordingly we found this procedure of particular use in the separation of glucose derivatives substituted in the 2-*O*-position from those with a free 2-hydroxyl group. Thus, 100% adsorption of 3-*O*-methyl-D-glucose from its aqueous solution in contact with the resin was observed in 2 hr. under the experimental conditions employed, while 2-*O*-methyl- and 2 : 3-di-*O*-methyl-D-glucose were adsorbed slowly and incompletely. Further, the importance of the furanose structure is demonstrated by the rapid and complete adsorption of 6-*O*-methyl-D-glucose in comparison with the weak adsorption of 4 : 6-di-*O*-methyl-D-glucose. As expected, 2 : 3 : 6-tri-*O*-methyl-D-glucose was adsorbed to an even smaller extent. It seems possible, however, that the slow adsorption of 2-substituted sugars (where complex formation at $C_{(1)} : C_{(2)}$ is precluded) could be explained by the participation of the open-chain form of the sugar (cf. Foster, *J.*, 1953, 982).

The same resin may also be used to separate suitable mixtures of glycosides, and, except for the cases reported by Chambers, Zill, and Noggle (*J. Amer. Pharm. Assoc.*, 1952, **41**, 461) which depended on differences in the aglycone group, gives the first example of this type of separation by an ion-exchange resin. The separation depends on the preferential adsorption of a component having a *cis*-glycol grouping and is demonstrated in the case of methyl α-D-gluco- and -manno-pyranosides. The slight adsorption of the glucoside in this case is noteworthy and, in view of its ready removal from the resin by washing with

water, probably accords with Foster's conclusion (*loc. cit.*) that formation of a stable 4 : 6-complex requires the presence of the open-chain form of the sugar. A further application to the separation of a glycoside (not having a *cis*-glycol group) from the parent aldose has been employed in the case of glucosides as a routine procedure in these laboratories for some time, and is preferred to the procedure of Roseman, Abeles, and Dorfman (*Arch. Biochem. Biophys.*, **1952**, **36**, 232) since degradation of the aldose by the basic form of the resin is avoided (cf. Phillips and Pollard, *Nature*, 1953, **171**, 41).

In all the observed cases, with the exception of methyl α-D-glucopyranoside, the sugars, when once adsorbed on the resin, were not readily removed by washing with water but were recovered in good yield by treating the resin with a solution of boric acid or sodium tetraborate, the former being preferred normally to avoid risk of alkaline degradation (cf., *e.g.*, Kenner and Richards, *J.*, **1954**, 278). The pure compound was then readily obtained by a development of the method of Zill, Khym, and Cheniae (*loc. cit.*).

The principles implied in the above are expected to be of general application to various types of mixtures which are commonly obtained in carbohydrate chemistry, and are well illustrated in the following improved preparation of 2-*O*-methyl-D-glucose. The latter compound has previously been prepared by several methods (Weygand and Trauth, *Chem. Ber.*, 1952, **85**, 57; Bourne and Peat, *Adv. Carbohydrate Chem.*, **1950**, **5**, 148), but each has involved a series of several reactions in order to block all hydroxyl groups except that on $C_{(2)}$. However, the known preferential reactivity of the 2-hydroxyl group compared with that at $C_{(3)}$ with alkaline reagents (Gaver *et al.*, U.S.P. 2,563,526, 1951; Heddle and Percival, *J.*, 1939, 249; Robertson and Griffith, *J.*, 1935, 1193), suggested that the partial methylation of methyl 4 : 6-*O*-benzylidene-α-D-glucoside should yield predominantly the 2-methyl ether. This was found to be the case and hydrolysis of the product yielded a mixture comprising mainly 2- and 3-*O*-methyl-D-glucoses with glucose, from a solution of which the last two components were readily removed by treatment with the borate resin as described above. Unfortunately, it was not possible to avoid the formation of a small amount of the 2 : 3-di-*O*-methyl derivative during the partial methylation and although pure 2-*O*-methyl-D-glucose could be obtained solely by separation with the borate resin, the yield was improved by use of cellulose column chromatography.

Experimental

Chromatographic separations, on Whatman No. 1 paper, were carried out with a solvent containing butan-1-ol–pyridine–water (6 : 4 : 3). The sprays used to reveal the sugars were: (a) silver nitrate (Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444); (b) *p*-anisidine hydrochloride (Hough, Jones, and Wadman, *J.*, 1950, 1702).

Preparation of the Borate Form of Amberlite Resin IRA-400.—A column of Amberlite resin IRA-400 (OH) (100 g.; 20—50 mesh) was washed with a solution of sodium tetraborate (0·1M; 5 l.), excess of borate removed by washing with water, and the resin collected by filtration and stored in a damp condition.

Adsorption of Sugars by Amberlite Resin IRA-400 (*borate*).—In typical experiments, the sugar (0·25 g.) was dissolved in water (28 ml.) and, if necessary, the solution was kept overnight to attain mutarotational equilibrium. The borate resin (5 g.) was added, the mixture shaken, and the adsorption of the sugar followed by measurement of optical rotation. In several cases the absence of rearrangement was demonstrated by evaporation of the equilibrium solution, the original compound being obtained in yield corresponding to the decrease in optical rotation. The behaviour of various sugars is recorded in the annexed Table.

Desorption of Sugars from Amberlite Resin IRA-400 (*borate*).—The resin carrying the adsorbed sugar was collected by filtration and washed (0·5 hr.) by shaking it with water (3 × 50 ml.). Examination of the washings showed that only in the case of methyl α-D-glucoside was the sugar completely eluted. However, prolonged shaking removed a small proportion (8% at equilibrium) of methyl α-D-mannoside. The resin was then shaken (1 hr.) with successive quantities of 0·5M-boric acid (50 ml.), until no further sugar was removed from the resin. The combined boric acid solutions were concentrated under reduced pressure and the residue was subjected to repeated distillation under reduced pressure with quantities (500 ml.) of redistilled methanol (cf. Zill, Khym, and Cheniae, *loc. cit.*). Complete removal of boric acid was demonstrated by electrical-conductivity measurements on an aqueous solution of the final residue.

The dried residue was weighed and crystallised by the addition of a few drops of absolute alcohol. In typical experiments crystalline 3-*O*-methyl-D-glucose was obtained (80%), while methyl α-D-mannoside (m. p. and mixed m. p. 192—193·5°) was recovered from the resin in 65% yield after only one washing with boric acid, both products being chromatographically pure.

Sugar	Rotational equilm. (hr.)	Adsorption (%) at equilm.
D-Glucose	2	100
D-Mannose	2	100
2-*O*-Methyl-D-glucose	>7	39
3-*O*-Methyl-D-glucose	2	100
6-*O*-Methyl-D-glucose	2	100
2 : 3-Di-*O*-methyl-D-glucose	>7	56
4 : 6-Di-*O*-methyl-D-glucose	>7	38
2 : 3 : 6-Tri-*O*-methyl-D-glucose	>7	8·5
Methyl α-D-glucopyranoside	3	33
Methyl α-D-mannopyranoside	3	95

Typical Separations using Amberlite Resin IRA-400 (*borate*).—(a) D-*Glucose and methyl* α-D-*glucopyranoside.* A mixture of 0·125 g. of each compound in water (28 ml.) was shaken for 4 hr. with Amberlite resin IRA-400 (borate) (5 g.), and the resin collected by filtration and washed with water (3 × 50 ml.; 2 hr. each). The filtrate and washings, on evaporation to dryness, afforded methyl α-D-glucoside (0·098 g., 78%) which crystallised completely, had m. p. and mixed m. p. 167·5—168·5°, and moved as a single component on the paper chromatogram. Chromatographically pure D-glucose (0·088 g., 70%) was obtained from the resin by elution with boric acid (4 × 50 ml.; 0·5M), as described above.

(b) *Methyl* α-D-*glucopyranoside and methyl* α-D-*mannoside.* A solution of 0·125 g. of each compound in water (28 ml.) was shaken overnight with Amberlite resin IRA-400 (borate) (5 g.). Methyl α-D-glucoside (0·087 g., 70%), obtained as described under (a), had m. p. 158—161° and was found (paper chromatography) to contain mannoside. A further brief treatment with the borate resin (1 g.) gave glucoside of m. p. and mixed m. p. 167·5—169° which contained a trace of mannoside. After removal of the last traces of glucoside with water, the resin yielded chromatographically pure methyl α-D-mannoside (0·070 g., 56%) which had m. p. and mixed m. p. 192—194°.

Preparation of 2-O-*Methyl*-β-D-*glucose.*—A solution of methyl 4 : 6-*O*-benzylidene-α-D-glucoside (20·0 g.) with sodium hydroxide (3·12 g.) in acetone (200 ml.) and water (40 ml.) was stirred and maintained at 45° while methyl sulphate (6·9 ml.) was added slowly during 1 hr. Thereafter the mixture was boiled under reflux for 30 min. (⟶ pH9), then poured into water (1 l.), and the resulting solution concentrated at 35° under reduced pressure until white needles of methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-methyl-α-D-glucoside began to separate (2·80 g.; m. p. and mixed m. p. 122—123° when recrystallised from water). After filtration the solution was adjusted to 1·0N with concentrated sulphuric acid, heated on the boiling-water bath for 20 hr., and concentrated under reduced pressure to 200 ml. An aqueous solution of barium hydroxide (95% of the calculated amount) was added to the hot solution, and neutralisation completed by addition of barium carbonate. Examination of the resulting solution by paper chromatography (sprays " a," " b ") showed the presence of glucose, 2-*O*-methyl-, 3-*O*-methyl-, and 2 : 3-di-*O*-methyl-D-glucose, in the proportion, estimated visually, of 6 : 4 : 1 : 1. Although the R_F values of the two monomethyl ethers were very similar the former was distinguished by its very slow and faint reaction with spray " a," whereas the latter behaved as a normal aldose towards this reagent. This phenomenon is characteristic of 2-ethers of aldoses (Kenner and Richards, personal communication) and will be discussed in detail later.

The neutralised solution was next de-ionised by stirring it with mixed Amberlite resins IR-120(H) and IR-4B(OH), and after filtration stirred for 1 hr. with Amberlite resin IRA-400 (borate form) (100 g.). The resulting solution was again de-ionised and evaporated to a colourless syrup (4·31 g.) which was shown by paper chromatography as above to be mainly 2-*O*-methyl-D-glucose, contaminated with a small amount of 2 : 3-di-*O*-methyl-D-glucose. A solution of the syrup in the minimum of boiling ethanol, when diluted with butan-1-ol (25 ml.) and kept at 0°, slowly deposited the crystalline 2-methyl ether (0·92 g.), showing m. p. 157—159° alone or in admixture with a sample prepared by the method of Weygand and Trauth (*loc. cit.*), $[\alpha]_D^{20}$ +65° (equil.; *c*, 1 in H_2O). A further quantity (0·88 g., total 12·5%) was obtained by evaporation of the liquors from the above crystallisation, followed by chromatography on powdered cellulose, with butan-1-ol followed by ethanol as eluant.

The p-*nitrophenylhydrazone*, prepared in the usual manner, showed m. p. 196—197° (Found: N, 12·9; OMe, 9·6. $C_{13}H_{19}O_7N_3$ requires N, 12·8; OMe, 9·4%).

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Carissone.

By W. A. AYER and W. I. TAYLOR.

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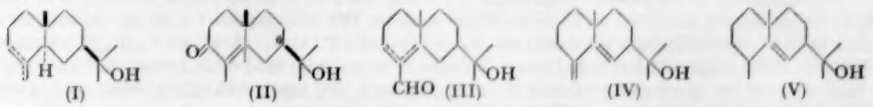
Eudesmol has been transformed into carissone which establishes the absolute stereochemistry of the latter compound as well as that of the cyperones.

KLYNE (*J.*, 1953, 3072), who applied the method of molecular-rotation differences to the sesquiterpenes, showed that the stereochemistry at the quaternary carbon atoms of eudesmol (I), selinene, and the cyperones are identical and the same as that at $C_{(10)}$ in the steroids. Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward (*J. Amer. Chem. Soc.*, 1954, **76**, 314) confirmed this by the synthesis of a derivative of eudesmol from a compound whose absolute stereochemistry is known. Barton and Tarlton (*J.*, 1954, 3492) showed that carissone (Mohr, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 462) must have structure (II) by converting it into α- and β-cyperone by dehydration under different conditions; however, the stereochemistry at $C_{(6)}$ remained undetermined We have now transformed eudesmol into carissone which establishes the absolute stereochemistry of the latter and proves experimentally the relation between the cyperone and the eudesmol group deduced by Klyne. Another proof of the stereochemistry of the cyperones has been given by McQuillin (*J.*, 1955, 528) from a consideration of the mechanism of their synthesis from (−)-dihydrocarvone.

Reaction of eudesmol with nitrosyl chloride, followed by treatment with a base, gave the αβ-unsaturated ketone oxime which after conversion into its 2 : 4-dinitrophenylhydrazone was indistinguishable from the authentic derivative of carissone kindly provided by Professor D. H. R. Barton. Oxidation of the crude alcoholic fraction obtained by the action of selenium dioxide on eudesmol also gave carissone, but by the action of peracetic acid on the sesquiterpene alcohol, followed by hydrolysis and oxidation, an isomeric ketone was formed. Its 2 : 4-dinitrophenylhydrazone with $\lambda_{max.}$ 380 mμ is consistent with the structure (III) but because of the low yield it has not been further investigated. These results show that the eudesmol used in this work was a mixture of *exo*- and *endo*-double-bond isomerides although chromatographed material was used.



(I) (II) (III) (IV) (V)

Among the products of the selenium dioxide oxidation was a crystalline diene which was stable to chromic oxide in pyridine and did not react with maleic anhydride. Its ultraviolet absorption maximum at 240 mμ and an infrared band at 870 cm.$^{-1}$ indicated the formula (IV) for the diene, and the resistance to attack by maleic anhydride is ascribed to steric hindrance by the neighbouring *iso*propyl group. On catalytic hydrogenation the diene took up one mol. of hydrogen and the band at 870 cm.$^{-1}$ disappeared; the product had an ultraviolet absorption spectrum typical of a trisubstituted double bond and therefore has structure (V).

[*Added July 15th*, 1955.]—Carissone 2 : 4-dinitrophenylhydrazone can be converted in good yield into carissone by Demaecker and Martin's method (*Nature*, 1954, **173**, 266).

Experimental

Carissone from Eudesmol Nitrosochloride.—Saturated methanolic hydrogen chloride (12 ml.) was added slowly with stirring to an ice-cold solution of eudesmol (3·5 g.) and ethyl nitrite (7 ml.) in methanol (10 ml.), then after 0·5 hr. the green solution was concentrated *in vacuo*, water was added and the whole extracted with ether, to give the crude nitrosochloride. This derivative in absolute ethanol (40 ml.) in which sodium (0·5 g.) was dissolved was refluxed for 0·5 hr., then diluted with water and neutralised with gaseous carbon dioxide, and the crude oxime (3·2 g.) extracted with ether. After chromatography over alumina, the oxime (0·5 g.; $\lambda_{max.}$ 243 mμ, ε 7000) was obtained in a purer state from the ether–methanol (20 : 1) eluate. Since the oxime did not crystallise it was hydrolysed by boiling ethanolic hydrochloric acid, and the resulting product converted into its 2 : 4-dinitrophenylhydrazone which after 4 crystallisations from chloroform–ethanol gave carissone 2 : 4-dinitrophenylhydrazone (0·2 g.), m. p. and mixed m. p. 176—177° which resolidified and melted again at 203—205°, $[\alpha]_D$ +450° (*c*, 0·04 in $CHCl_3$) (Found: N, 13·0. Calc. for $C_{21}H_{26}O_5N_4$: N, 13·4%). The ultraviolet absorption spectrum in EtOH had $\lambda_{max.}$ 390 mμ (ε 24,000), and the infrared spectrum was identical with that of an authentic sample.

Carissone by Selenium Dioxide Oxidation of Eudesmol.—Eudesmol (10 g.) and selenium dioxide (6 g.) in benzene (100 ml.) were stirred vigorously and refluxed for 4 hr., then filtered hot. The solvent was removed. The residue (12·6 g.) was chromatographed over alumina and from the benzene–light petroleum (b. p. 60—80°) eluate a solid (3·8 g.) was isolated which after crystallisation from ethanol–water or acetone–water gave the pure *diene* (IV), m. p. 108—109°, $\lambda_{max.}$ 240 mμ (ε 24,000) (Found: C, 81·5; H, 11·2. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%). Further elution of the column with benzene–methanol gave a low-melting glass (5 g.) which was treated with chromic oxide (1·5 g.) in pyridine (40 ml.). The solution was kept at room temperature for 4 hr. After addition of water, the crude oxidation product was isolated by extraction with ether and converted into the 2 : 4-dinitrophenylhydrazone in the usual way. The derivative was purified by chromatography over alumina and eluted with benzene–chloroform (1 : 1), to afford carissone 2 : 4-dinitrophenylhydrazone (750 mg.), m. p. 170°, raised after one crystallisation from chloroform–ethanol to constant m. p. 176—177° (Found: N, 13·4%).

Peracetic Acid Oxidation of Eudesmol.—To eudesmol (15 g.) in acetic acid (85 ml.) containing concentrated sulphuric acid (1 ml.), 30% hydrogen peroxide (8 ml.) was slowly added during 0·5 hr. The mixture was cooled during the addition with water, then warmed to 40° for 4 hr. Next morning the solution was poured into water containing ferrous sulphate, and an ether extract, after being washed with water, was concentrated. The residue was refluxed with 10% ethanolic potassium hydroxide for 1 hr., then extracted once again into ether, washed with water, dried, and distilled. The fraction (3·3 g.), b. p. 105—115°/0·1 mm., was treated with chromic oxide (1·6 g.) in pyridine (17 ml.) at room temperatrure for 3 hr. The crude oxidation product (2·6 g.) was converted into its 2 : 4-dinitrophenylhydrazone which was purified by chromatography over alumina. The chloroform–methanol eluate gave material of m. p. 80—85°, whence the pure *derivative* (40 mg.) was obtained after 7 recrystallisations from methanol and ethanol; it had m. p. 116—118° with softening at 102°, $\lambda_{max.}$ 380 mμ (ε 23,700) (Found: C, 60·3; H, 6·9; N, 13·5. $C_{21}H_{28}O_5N_4$ requires C, 60·6; H, 6·8; N, 13·4%).

Hydrogenation of the Diene.—The diene (IV) took up 1 mol. of hydrogen in ethanol in the presence of Adams catalyst, and the resulting *monoene* (V) was obtained pure (m. p. 76—78°) after several crystallisations from ethanol–water (Found: C, 81·0; H, 11·5. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%). The infrared spectrum was different from that of eudesmol and its ultraviolet absorption spectrum had at 220, 210, 205, and 200 mμ ε 835, 2700, 3880, and 4500 respectively (cf. Bladon *et al.*, *J.*, 1952, 2737).

We are very much indebted to Mr. H. V. Marr of Plaimar Ltd., Western Australia, for the isolation and partial purification of eudesmol, and to Mr. L. G. Humber of this Department for the further purification of this material by chromatography. The infrared spectral analyses were performed by Mr. W. Fulmor and his staff, Lederle Laboratories Division, American Cyanamid Company. We are grateful to the National Research Council of Canada for a grant and for a N.R.C. bursary to one of us (W. A. A.).

University of New Brunswick, Canada. [*Received, April 16th*, 1955.]

The Low-temperature Oxidation of iso*Butane. The Progressive Accumulation of Products and Consumption of Reagents.*

By J. J. Batten, H. J. Gardner, and M. J. Ridge.

[Reprint Order No. 6271.]

The progressive accumulation of products and consumption of reagents during the oxidation of *iso*butane at 291° have been studied. During the induction period (12·5—60 min. depending upon conditions) small but appreciable quantities of reactants are converted into products. There is a significant difference in the distribution of products during and after the induction period, indicating a difference in mechanism. It is suggested that the reaction during the induction period is surface-inhibited and probably proceeds by straight chains. The amounts of higher aldehydes, total peroxides, and to a smaller extent of formaldehyde, reach pronounced maxima at the maximum rate of pressure rise. The evidence does not exclude the participation of alkyl peroxides or peroxy-radicals in the reaction. The formation of acetone indicates tertiary attack on *iso*butane.

The reaction between hydrocarbon vapours and oxygen is autocatalytic. There is an induction period of little or no change in pressure, which may extend for hours, followed by a period of accelerating increase in pressure. Hydrocarbons containing three or more carbon atoms show different mechanisms at high and at low temperatures. It is generally accepted that both modes of oxidation are degenerate branching-chain reactions (Semenov, "Chemical Kinetics and Chain Reactions," Oxford Univ. Press, 1935), *i.e.*, chain reactions in which branching takes place through a relatively stable intermediate. There is, however, little agreement regarding details of mechanisms proposed for hydrocarbon–oxygen reactions and in particular the identity of the intermediate responsible for degenerate branching is still under discussion. For the low-temperature reaction two classes of compound have been suggested, *viz.*, organic peroxides, particularly hydroperoxides (Ubbelohde, *Proc. Roy. Soc.*, **1935**, *A*, **152**, 354; Hinshelwood, *Discuss. Faraday Soc.*, 1947, **2**, 111; Walsh, *Trans. Faraday Soc.*, 1946, **42**, 269) and aldehydes (Norrish, XVI Internat. Colloquium, Centre National de la Recherche Scientifique, Paris, p. 16; Knox and Norrish, *Proc. Roy. Soc.*, **1954**, *A*, **221** 151). At present it is difficult to decide which of these theories of degenerate branching is to be accepted, and additional definite information is needed regarding the progressive formation of products and consumption of reagents during hydrocarbon–oxygen reactions.

Results for the oxidation of *iso*butane are now presented. Particular attention has been directed to the earlier stages of the reaction, where the process may be expected to be less complicated by the reactions of products, and unambiguous information should be more readily obtained than from the region of the maximum rate of pressure change.

For a study of the mechanism of its oxidation, *iso*butane has several attractive features. For instance, its molecule contains nine primary and one, weaker, tertiary C–H bond. Consequently, the predominant point of attack on the hydrocarbon during oxidation is probably known. Also, the hydroperoxide (*tert.*-butyl) derived directly from *iso*butane is comparatively stable to heat and should be readily determined.

The autoxidation of *iso*butane has been studied by Pease (*J. Amer. Chem. Soc.*, 1929, **51**, 1839) who by a flow method found methane, hydrogen, carbon monoxide, carbon dioxide, and unsaturated substances among the products. Analyses were made for gaseous products only, and the lowest temperature studied was 350°. The ignition diagram of *iso*butane has been determined by Townend (*Chem. Rev.*, 1937, **21**, 268).

Experimental

The apparatus and procedure were those described by Mulcahy and Ridge (*Trans. Faraday Soc.*, 1953, **49**, 906). The induction period was defined as the time required for the rate of pressure increase to reach 0·5 mm./min.

Materials.—*iso*Butane (Phillips Petroleum Company, Pure Grade, 99%) was passed through

soda–asbestos and condensed in liquid air. After being degassed it was subjected to two trap-to-trap distillations, generous first and last portions being rejected. The fraction retained was passed through phosphoric oxide before storage. Commercial (medical grade) oxygen was used after passage through phosphoric oxide and liquid-air traps.

The formaldehyde solution used in the polarographic work was prepared by heating paraformaldehyde and dissolving the evolved gas in water. Formaldehyde peroxide (m. p. 57—59°) was prepared according to Wieland and Wingler (*Annalen*, 1923, **431**, 301). *tert.*-Butyl hydroperoxide was prepared by extracting a commercial material with aqueous sodium hydroxide and regenerating the peroxide with hydrochloric acid. Reagent-grade hydrogen peroxide was used.

Analysis.—The mixture formed was analysed quantitatively for *iso*butane, oxygen, methane, C_2 hydrocarbons, carbon monoxide, carbon dioxide, total peroxide, acetone, formaldehyde, total aldehydes, higher aldehydes (by difference), and acids.

Samples were taken by connecting the reaction vessel to an evacuated sampling vessel (450 ml.) at −80° (acetone–carbon dioxide). The volatile components were then admitted to an analysis system which included a LeRoy–Ward still (LeRoy, *Canad. J. Res.*, 1950, *B*, **28**, 492), McLeod gauge, Töpler pump, and gas burette. When it was desired to determine condensable products, the samples were taken with 10—15 ml. of a suitable solvent in the sampling vessel.

Volatile components were determined by cutting the sample into three fractions by pumping off with the Ward still at (1) −196° (liquid nitrogen), (2) −170°, and (3) *ca.* −110°.

Oxygen, carbon monoxide, and methane were determined by combustion of fraction (1) in a Cu–CuO furnace fitted with a liquid-air trap (Marcotte and Noyes, *Discuss. Faraday Soc.*, 1951, **10**, 236). In this furnace carbon monoxide was oxidized to carbon dioxide, hydrogen to water, and oxygen was removed as copper oxide. Methane was measured as an uncondensable residue. On replacement of the liquid-air trap by an acetone–carbon dioxide trap, carbon dioxide was evaporated, pumped off, and measured. When the trap was warmed to room temperature any water (never more than a trace) could be detected. Oxygen was determined by difference. Ethane and ethylene occur in fraction (2), which was negligible in all cases. *iso*Butane and carbon dioxide constitute fraction (3). Carbon dioxide was absorbed in a soda–asbestos thimble and determined by difference. The residue was taken as *iso*butane.

The methods for the determination of total peroxide, total aldehyde, formaldehyde, and acid have already been described (Mulcahy and Ridge, *loc. cit.*). Acetone was determined by the hydroxylamine hydrochloride method on a sample which had been passed through a silver oxide column to destroy aldehydes.

To gain information regarding the components of the " total peroxides," the reaction products were subjected to polarographic examination.

Polarographic procedure. Samples were taken with distilled water or a solution of the supporting electrolyte in the cold sampling vessel. Current–voltage curves were obtained by using Lingane and Kolthoff's three-electrode circuit (*J. Amer. Chem. Soc.*, 1939, **61**, 825) with a device for reproducible liquid junctions (Gardner and Diamantis, *Austral. J. Sci.*, 1951, **14**, 23). The saturated calomel electrode was prepared, the precautions mentioned by Hills and Ives (*J.* 1951, 301) being observed, and was 0·244 v *versus* the hydrogen electrode of unit activity at 25°. The rate of mercury flow was 1·42 mg. sec.$^{-1}$; the drop time had the following values for the given potentials: −0·5 v, 3·75 sec.; −1·0 v, 3·5 sec.; −2·0 v, 2·8 sec.

Reaction Conditions.—The reaction was studied in oxygen-rich (A) and hydrocarbon-rich (B) mixtures. Owing to fluctuations in the activity of the reaction vessel, slight modifications had to be made from time to time in the compositions of the actual mixtures used, which were:

Mixture	*iso*Butane (mm.)	Oxygen (mm.)	Nitrogen (mm.)	Mixture	*iso*Butane (mm.)	Oxygen (mm.)	Nitrogen (mm.)
A 1	80	350	—	B 1	200	100	—
2	70	350	—	2	150	100	350

All experiments were carried out at 291°.

Results.

The decline in the concentrations of the reagents, the pressure rise, and the accumulation of products for mixtures A and B are shown in Figs. 1—6. The quantities are expressed in mm. of partial pressure in the reaction vessel at the reaction temperature. The reaction vessel used to obtain the results shown in Figs. 3 and 6 was destroyed by an explosion. A second, similar vessel was used for all other results. The shapes of the pressure curves indicate that the change in reaction vessel has not altered the type of the reaction.

There is an interesting difference in the shapes of the curve of pressure increase for mixtures A and B. In hydrocarbon-rich mixtures (type B) the rate of pressure change does not pass through a smooth maximum and tail off, as it does with oxygen-rich mixtures (type A), but abruptly falls to zero after a period of vigorous acceleration. In the first reaction vessel this halt occurred so sharply that no transition could be detected between a state of accelerating

FIG. 1. iso*Butane, oxygen, carbon dioxide, carbon monoxide, and methane concentrations, and pressure rise* v. *time, for* 80 *mm. of* isobutane + 350 *mm. of oxygen* (A, 1).

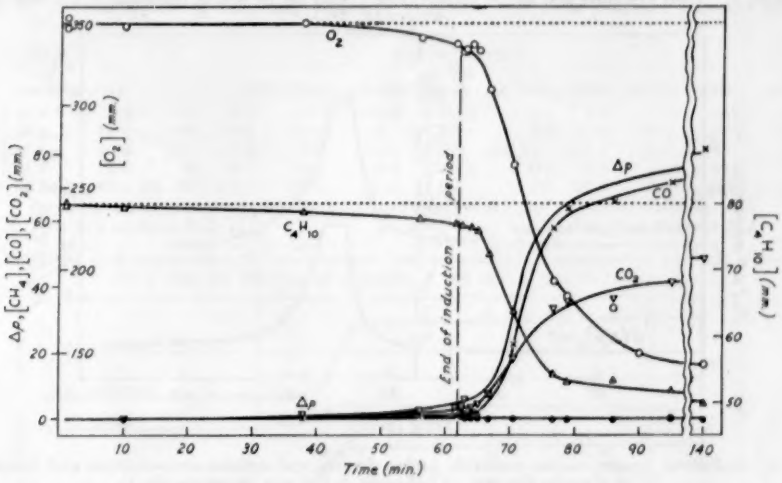
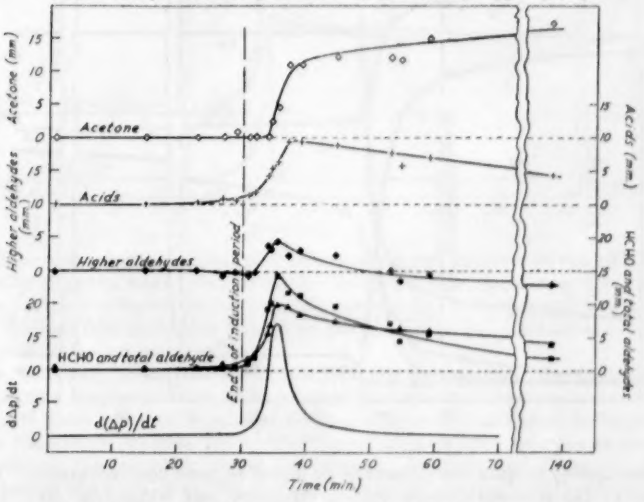


FIG. 2. *Acetone, acid, higher aldehyde, total aldehyde, and formaldehyde concentrations, and rate of pressure rise* v. *time for* 80 *mm. of* isobutane + 350 *mm. of oxygen* (A, 1).



pressure increase and that of constant pressure (see Fig. 6). In the second vessel there was a short period (0·5 min.) of slackening reaction rate (see arrow in Fig. 5).

Figs. 4, 5, and 6 show that the halt in pressure increase reflects a general cessation of reaction when the oxygen concentration has been reduced to a low figure. This discontinuous change in direction of the upward-curving Δp *versus* time curve indicates that chain branching is independent of oxygen concentration down to very low partial pressures.

Table 1 gives pressures of products and the decreases in the reactants, (*a*) at the end of the

induction period (θ) for both reaction mixtures, (*b*) at the maximum rate of pressure change ($\rho_{max.}$) for mixture A, and at the halt in pressure increase for mixtures B, and (*c*) near the completion of reaction for mixture A.

Consumption of Reagents.—By the end of the induction period the amounts of reagents consumed indicate that appreciable reaction has occurred (see Table 1). For both mixtures A and B the ratios of the quantities consumed are approximately the same ($-\Delta O_2/-\Delta RH = 2{\cdot}2$

FIG. 3. *Total peroxides and rate of pressure rise* v. *time for* 70 *mm. of* isobutane + 350 *mm. of oxygen* (A, 2).

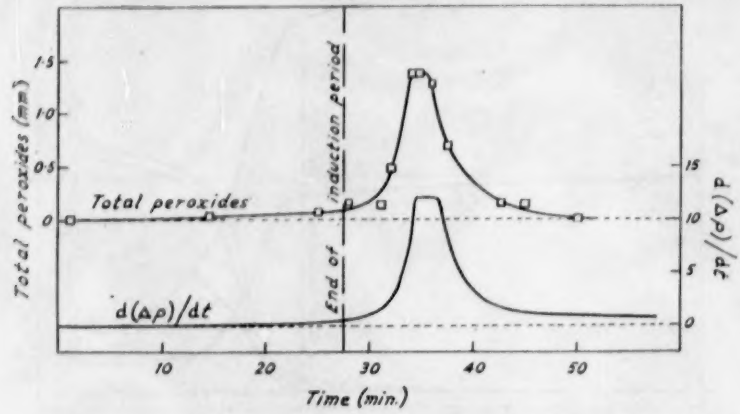
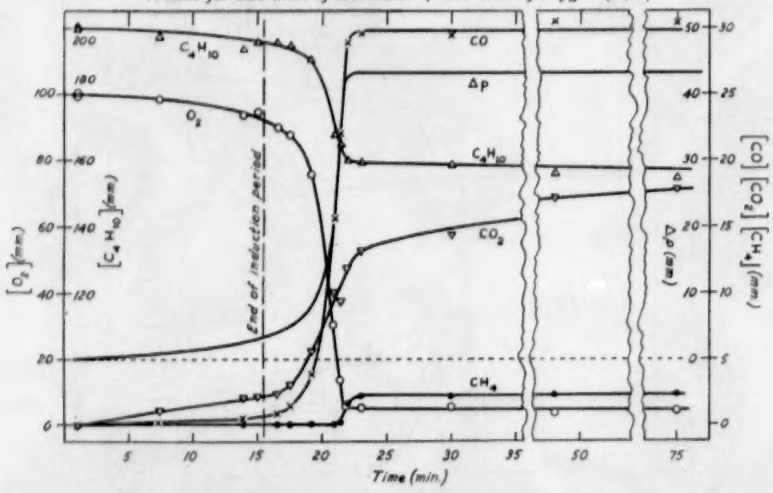


FIG. 4. isoButane, *oxygen, carbon monoxide, carbon dioxide, and methane concentrations and pressure rise* v. *time for* 200 *mm. of* isobutane + 100 *mm. of oxygen* (B, 1).



and 1·6, respectively) despite the difference in initial reagent concentrations. This is similar to behaviour in the propene–oxygen system (Mulcahy and Ridge, *loc. cit.*). However, the absolute amounts of each reagent consumed appear to vary more with initial concentration of the reagents than was the case with propene. In both systems the absolute amounts of reagents consumed by the end of the induction period are approximately the same.

After the induction period the ratio $-\Delta O_2/-\Delta RH$ for mixtures A increases somewhat until at the maximum rate it is about 2·6. Near the completion of the reaction it reaches 3·4. In mixture B the ratio has reached 2·3 when the pressure becomes constant. The increase in this ratio is due to the increasing importance of the oxidation of products as the reaction progresses.

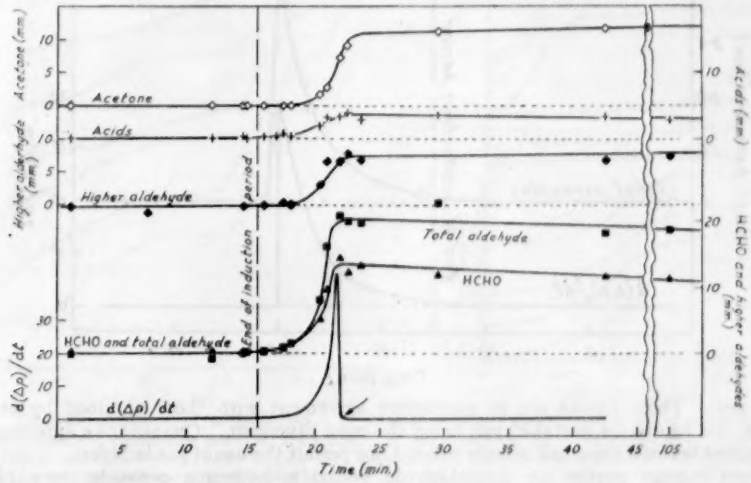
Formation of Products.—The products fall into two classes : (*a*) Compounds such as carbon monoxide and dioxide, acetone, acids, etc., which gradually accumulate as the reaction proceeds and represent the debris of the reaction chains. (*b*) Transient products such as peroxide, higher aldehyde, and formaldehyde whose concentrations build up to a maximum at the maximum rate, and which readily undergo reaction in the environment in which they are produced. These are vital intermediates in the reaction chains and one of them is probably responsible for degenerate branching.

TABLE 1. *Consumption of reagents, yields of products, and total pressure increase during reaction.*

Mixture	Stage of reaction	Pressure (mm.) Δp	$-\Delta O_2$	$-\Delta RH$	ΔCH_2O	$\Delta R{\cdot}CHO$	Total perox.	$\Delta COMe_2$	ΔCO	ΔCO_2	ΔCH_4	ΔAcid
A 1	at θ *	4·8	14	6·2	1·0	−0·5	0·1 ‡	0·0	1·0	3·0	0·0	1
	at $\rho_{max.}$	34·0	90	34·5	10·0	4	1·4	6·0	25·0	19·5	0·0	6
	at t_∞	80·5	207	60·5	3·8	−2·0	0·0	*ca.* 16	81·5	49·0	0·0	4
B 1	at θ	3·0	8	5	0·3	0·0	0·1 †	0·0	0·6	2·2	0·0	0·1
	at halt	43·1	*ca.* 95	41	13·5	7·2	4·2	7·5	29·8	13·2	2·2	3

* θ means end of induction period; $\rho_{max.}$, maximum rate; and t_∞ end of reaction.
† Reaction mixture A 2. ‡ Reaction mixture B 2.

FIG. 5. *Acetone, acid, higher aldehyde, total aldehyde, and formaldehyde concentrations, and rate of pressure rise* v. *time for* 200 *mm. of* iso*butane* + 100 *mm. of oxygen* (B, 1).



The close association between total peroxide content and the rate of reaction is shown in Fig. 3. The $d\Delta p/dt$ curve has a plateau at the maximum rate, indicating the attainment of a steady state. This is reflected in the peroxide curve. In the hydrocarbon-rich mixture the total peroxide content falls sharply to zero when the reaction stops, emphasizing the short-lived nature of peroxide in the reaction system.

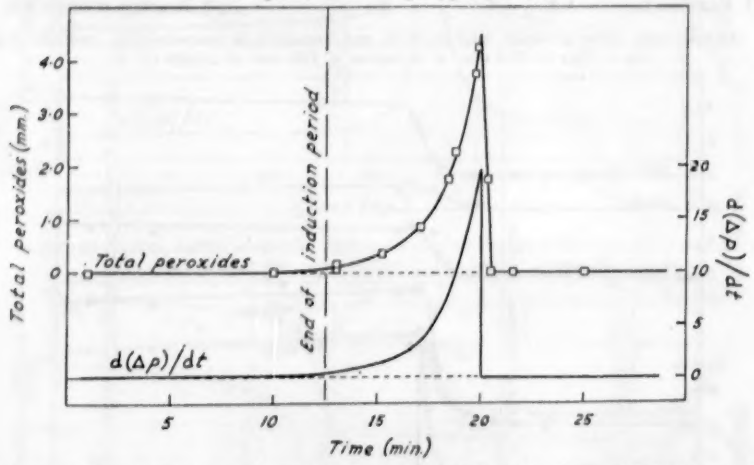
During the induction period the distribution of products is radically different from that in the region of the maximum rate. The earliest products detected are carbon dioxide and formaldehyde and these represent a considerable degradation of the original *iso*butane molecule. The shapes of the carbon dioxide *versus* time curves suggest that this gas is produced at a constant rate during the induction period (cf. propene; Mulcahy and Ridge, *loc. cit.*). After the induction period the yield of carbon monoxide increases sharply and rapidly out-strips the yield of dioxide. Higher aldehydes likewise become important after the end of the induction period. Fig. 1 demonstrates that a close connection exists between the rate of carbon monoxide production and the rate of pressure rise.

A polarographic study shows that the peroxidic products consist of hydrogen peroxide and aldehyde peroxides, and strongly suggests the presence of *tert.*-butyl hydroperoxide and other alkyl peroxides.

Polarographic Examination of Reaction Products.—Current–voltage curves for the reaction

products of 200 mm. of *iso*butane and 100 mm. of oxygen, recorded for various supporting electrolytes, are shown in Fig. 7 (the reaction was taken to 6 min. past the induction period, and the products were made up to 25 ml.). The waves which extend from 0·0 to −1·2 v *versus* the standard calomel electrode, cover the potential region where peroxides are expected to yield waves (Shtern and Polyak, *Acta Physicochim., U.R.S.S.*, 1939, **11**, 797; Knox and Norrish, *loc. cit.*). The lowered height in lithium hydroxide solution is probably due to ionization (see Everett and Minkoff, *Trans. Faraday Soc.*, 1953, **49**, 410). The waves with half-wave potentials at −1·5 to −1·6 v in the various solutions correspond in height and position to that expected for formaldehyde (Kolthoff and Lingane, "Polarography," Interscience Publ. Inc., New York, 2nd Ed., 1952). The wave at −1·88 v in 0·01 and 0·1M-LiOH (curves *e* and *f*) is probably due to acetaldehyde, and that at −1·83 v in 0·1M-LiCl (curve *a*) to acetaldehyde plus formic acid (see Kolthoff and Lingane, *op. cit.*). By comparison with the curve for a standard solution of formaldehyde (Fig. 8) and by reference to the published data for acetaldehyde and formic acid, it was estimated that the reacting mixture contained *ca.* 10 mm. of formaldehyde, *ca.* 0·5 mm. of acetaldehyde, and *ca.* 1·2 mm. of formic acid. The partial pressure of total peroxide was

FIG. 6. *Total peroxide and rate of pressure rise* v. *time for* 150 *mm. of* isobutane + 350 *mm. of nitrogen* + 100 *mm. of oxygen* (B, 2).



ca. 1·7 mm. These figures are in qualitative agreement with those obtained by chemical methods, the figures for acetaldehyde being the most divergent. Quantitative agreement was not expected because the small sample size did not permit the use of gas bubblers.

Current–voltage curves for formaldehyde peroxide, hydrogen peroxide, formaldehyde, *tert.*-butyl hydroperoxide, and the reaction mixture are shown in Fig. 8.

The fresh solution of formaldehyde peroxide (0·44 mM) yielded two waves with half-wave potentials at −0·3 v and −0·9 v respectively (curve *b*). Merely upon letting the solution stand for a few hours (curve *c*), or alternatively by shaking it with mercury (curve *d*), the current–voltage curve changed in character, the wave at −0·3 v disappearing. By comparing curve *d* with *e* and *f* the decomposed solution was estimated to contain *ca.* 0·45 mM-hydrogen peroxide and *ca.* 0·5 mM-formaldehyde. Removal of the hydrogen peroxide by titanium chloride and ammonia (MacNevin and Urone, *Analyt. Chem.*, 1953, **24**, 1760) yielded wave *h*, which is similar in shape to the curve *g* obtained for commercial "AnalaR" formaldehyde.*

* The decomposition of formaldehyde peroxide solution was investigated by using the colour reaction of hydrogen peroxide with titanium chloride. Hydrogen peroxide was detected within an hour of preparation. However, any handling, particularly where mercury was involved, as was the case with the polarographic cell, resulted immediately in the solutions' yielding the colour typical of hydrogen peroxide, when treated with titanium chloride. A colorimetric estimation gave *ca.* 0·5 mM-hydrogen peroxide (originally 0·44 with formaldehyde peroxide). From these experiments it is concluded that the curves obtained by Shtern and Polyak (*loc. cit.*) and Knox and Norrish (*loc. cit.*) for formaldehyde peroxide and probably other aldehyde peroxides are largely due to hydrogen peroxide and free aldehyde. The decomposition of formaldehyde peroxide to give hydrogen peroxide and formaldehyde has already been observed (Wieland and Wingler, *loc. cit.*). Our results indicate that metallic mercury catalyses this reaction, which is the reverse of that producing the peroxide from formaldehyde and hydrogen peroxide.

Advantage was taken of the effect of mercury on formaldehyde peroxide (and probably other aldehyde peroxides) in an attempt to determine alkyl hydroperoxides in the reaction mixture. The solution of products was shaken with mercury, and hydrogen peroxide then removed by treatment with titanium chloride and ammonia (see curves *k* and *j*, Fig. 8). The difference in height between curves *k* and *j* should correspond to the total hydrogen peroxide present (0·7 mm. in the reaction vessel).

Curve *j* probably represents those peroxides which are stable for a few hours in contact with mercury. Its shape suggests that at least two peroxides are present, and comparison with curve *i* shows that the wave between 0·0 and −0·55 v is probably due to *tert.*-butyl hydroperoxide (0·7 mm. in the reaction vessel). The remainder of the wave should then be due to other alkyl peroxides.

FIG. 7.

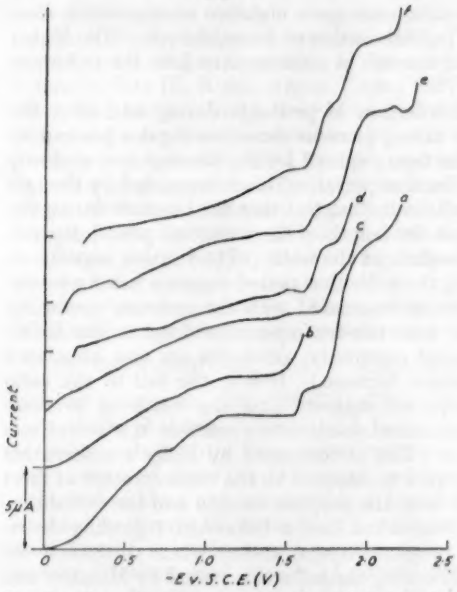


FIG. 8.

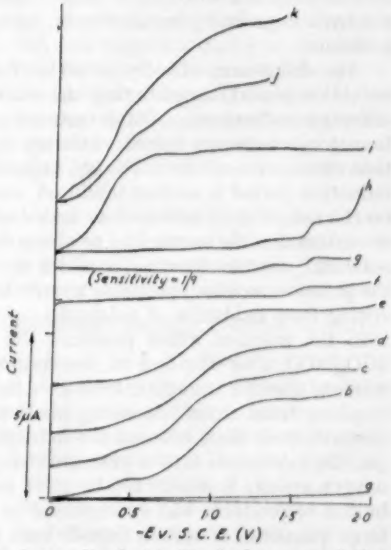


FIG. 7. *Current–voltage curves for the oxidation products of* isobutane *dissolved in 25 ml. of aqueous solution. The supporting electrolytes are :* (*a*) 0·1M-LiCl ; (*b*) 0·1M *(each) acetic, phosphoric, and boric acid, and* NaOH *to make* pH 4·5 ; (*c*) *as for* (*b*), pH 7·7 ; (*d*) *as for* (*b*), pH 11·5 ; (*e*) 0·01M-LiOH ; (*f*) 0·1M-LiOH. *Zero current for each curve is indicated.*

FIG. 8. *Polarograms for various peroxides in* 0·1M-LiCl : (*a*) *residual current ;* (*b*)—(*d*) 0·44mM-*formaldehyde peroxide ;* (*b*) *fresh solution ;* (*c*) *after* 10 *min. in cell ;* (*d*) *after shaking with mercury ;* (*e*) 0·39mM-*hydrogen peroxide ;* (*f*) 1·15mM-*formaldehyde prepared as described ;* (*g*) 0·45mM-*commercial "AnalaR" formaldehyde ;* (*h*) *formaldehyde peroxide treated with* $TiCl_4$ *and aq.* NH_3 ; (*i*) 0·5mM-tert.-*butyl hydroperoxide ;* (*j*)—(*h*) *oxidation products of* isobutane *dissolved in 25 ml. and shaken with mercury,* (*h*) *before further treatment,* (*j*) *after addition of* $TiCl_4$ *and* NH_3. *Zero current for each curve is indicated.*

From these results it is seen that hydrogen peroxide and its derivatives, although important constituents, may not amount to 50% of the total peroxides.* This is contrary to the findings by Knox and Norrish (*loc. cit.*) for the low-temperature oxidation of propane.

DISCUSSION

Under hydrocarbon-rich conditions methane makes a sudden appearance as a product when the consumption of oxygen is almost complete (see Fig. 4). In no case was methane

* A study of the rates of decomposition of the residual peroxide after treatment with mercury and titanium chloride, and of *tert.*-butyl hydroperoxide added to the treated solution of reaction products, as measured by the current at −0·6 v, supported the conclusion that *tert.*-butyl hydroperoxide occurs in the oxidation products.

detected when the system contained substantial quantities of oxygen (see Fig. 1). This suggests the presence of methyl radicals in the reacting mixture. The formation of acetone in conjunction with methyl radicals suggests the occurrence of *tert.*-butoxy-radicals, which are known to decompose thus: $(CH_3)_3C{\cdot}O{\cdot} \longrightarrow (CH_3)_2C{:}O + CH_3{\cdot}$. This evidence for *tert.*-butoxy-radical strengthens the case for the presence of *tert.*-butyl hydroperoxide, as it is likely that *tert.*-butoxy-radicals arise from the decomposition of a related peroxide or peroxy-radical.

The acetone found is evidence for tertiary attack on the hydrocarbon molecule. This is to be expected from the known reactions of *iso*butane. At the completion of the reaction the ratio $\Delta COMe_2/-\Delta RH$ is *ca.* 0·2 for both conditions of concentrations studied.

At the maximum rate of pressure change, *i.e.*, when the concentration of higher aldehyde is a maximum, the ratio Δ R·CHO/$-\Delta$RH is *ca.* 0·12. At the completion of the reaction the procedure for the estimation of higher aldehydes gave negative results which were undoubtedly due to effects arising from the polymerisation of formaldehyde. The higher aldehyde is probably acetaldehyde, formed as a result of primary attack on the *iso*butane molecule.

The difference, already noted in the distribution of products during and after the induction period, suggests that the reactions taking place in these two regions proceed by different mechanisms. Other factors than the time required for the development of slowly branching chains are operative during the induction period. This is supported by the fact that effects of inert gases (Ridge, unpublished results) suggest that the reaction during the induction period is surface-inhibited, and that the length of the induction period depends on the rate of destruction of an active intermediate at the walls. The relative importance of carbon dioxide among the products during the induction period suggests heterogeneous reaction. Carbon monoxide, which is obviously associated with the reaction producing the pressure increase, probably results largely from the decomposition of the radical R·CO· arising from oxidation of aldehydes. (As noted previously, aldehydes are also associated with the reaction which produces the pressure increase.) Hence, the fall in the ratio $\Delta CO_2/\Delta CO$ after the end of the induction period suggests that the onset of pressure increase marks a transition from a surface-dominated reaction to a reaction in which effects resulting from chain branching predominate. This is confirmed by Ridge's observation (unpublished) that, whereas the induction period is sensitive to the concentration of inert gas, the maximum rate of pressure change in both the propene–oxygen and the *iso*butane–oxygen system is unaffected by inert gas. Somewhat similar behaviour regarding distribution of products was encountered in the propene–oxygen system where comparatively large quantities of carbon dioxide were found during the induction period by Mulcahy and Ridge (*loc. cit.*): these authors, however, did not determine carbon monoxide.

The results show to a first approximation that the partial pressure of carbon dioxide increases linearly during the induction period. Whether or not carbon dioxide is in fact produced largely by a heterogeneous reaction during the early stages of the reaction, its constant rate of accumulation during the induction period implies that the reaction during the induction period proceeds by unbranched chains. This reaction also produces the active intermediate responsible for initiating the eventual autocatalytic reaction which produces the main pressure increase and the conversion of the bulk of the reactants.

From the available evidence it is not possible to determine the identity of this active intermediate. Higher aldehydes are present in significant quantities from the end of the induction period onwards, and the reaction evidently involves peroxides, although the quantities of hydroperoxide present are comparatively small. Experiments in which the reaction was interrupted by the withdrawal of the reactants and the treated reaction mixture subsequently fed back into the reaction vessel, indicate that peroxides in their normal state are not the substances responsible for the termination of the induction period in the low-temperature oxidation of hydrocarbons (Batten and Ridge, *Austral. J. Chem.*, in the press).

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Researches on Polyenes. Part III. The Synthesis and Light Absorption of Dimethylpolyenes.*

By P. Nayler and M. C. Whiting.

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A general synthesis of dimethylpolyenes (I) is described [namely, reduction of the diols (II) with lithium aluminium hydride]; the ultraviolet absorption spectra observed are compared with predictions made by means of molecular-orbital calculations.

The synthesis of the dimethylpolyenes (I), a series of especial interest in view of present theoretical attempts to correlate electronic absorption spectra with constitution, was attempted by R. Kuhn and Grundmann (*Ber.*, 1938, **71**, 442). They obtained the members where $n = 3$ and 4, and a concentrate of the compound (I; $n = 6$) for which the spectroscopic-intensity data (R. Kuhn, *Angew. Chem.*, 1937, **50**, 703) now suggest a purity of about 35%. Blout and Fields later (*J. Amer. Chem. Soc.*, 1948, **70**, 189) reported more accurate spectroscopic data for the two members (I; $n = 4$ and 6), prepared by Kuhn's method, and Bohlmann (*Chem. Ber.*, 1952, **85**, 386) reported a synthesis of the dodecapentaene (I; $n = 5$) and the preparation of material believed to contain the higher member (I; $n = 9$). [Data attributed by Barany, Braude, and Pianka (*J.*, 1949, 1898) to the compound where $n = 8$ apparently refer to dihydro-β-carotene.]

Bates, Jones, Nayler, and Whiting (unpublished work) found that 1 : 4-diphenylbut-2-yne-1 : 4-diol gave a moderate yield of 1 : 4-diphenylbuta-1 : 3-diene when treated with lithium aluminium hydride. The application of this method to glycols of type (II), which are easily accessible by one- or two-step condensation of acetylene with the well-known

(I) $CH_3{\cdot}[CH{=}CH]_n{\cdot}CH_3$ $CH_3{\cdot}[CH{=}CH]_a{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}[CH{=}CH]_b{\cdot}CH_3$ (II)

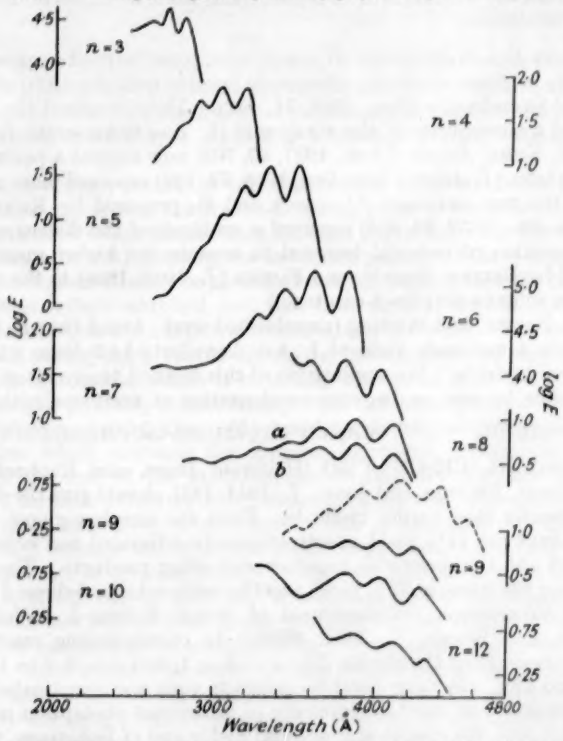
polyene aldehydes, $CH_3{\cdot}[CH{=}CH]_a{\cdot}CHO$ (Heilbron, Jones, and Raphael, *J.*, 1944, **136**; Cymerman, Heilbron, Johnson, and Jones, *J.*, 1944, 141), should give the dimethylpolyenes (I) more conveniently than earlier methods. Even the simplest glycol (II; $a = b = 0$) gave hexa-2 : 4-diene (*ca.* 11% yield, spectroscopically estimated and isolated as its maleic anhydride adduct and tetrabromide), together with other products. The next glycol (II; $a = 1$, $b = 0$) gave the triene in 32% yield, together with octa-4 : 6-diene-2 : 3-diol, presumably formed by anionotropic rearrangement of octa-3 : 6-diene-2 : 5-diol (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089). In corresponding reactions, giving the tetraene and pentaene from the glycols (II; $a = b = 1$, and $a = 2$, $b = 1$, respectively) in yields of 25% and 15%, the more polar by-products were not investigated; the hydrocarbons were recrystallised to constant intensity of ultraviolet absorption maxima, the positions agreeing well with the results of Blout and Fields and of Bohlmann, respectively (*locc. cit.*). Approximate analytical data, and infrared absorption spectra (see below) consistent with structure (I), were also obtained. For the hexaene (I; $n = 6$) prepared from the diol (II; $a = b = 2$) in markedly reduced yield, it was not possible to reach constant $\varepsilon_{max.}$ values, although the very high intensities observed (see below) for the purest specimen implied that it was essentially pure.

The higher dimethylpolyenes, where $n = 5$ and 6, polymerise rapidly, even in nitrogen, and are sparingly soluble in organic solvents; it was clear that in attempts to extend the series beyond $n = 6$ the experimental difficulties of manipulation would increase rapidly, and it would be necessary to handle these compounds almost entirely as dilute solutions, relying on the characteristic ultraviolet absorption spectra for identification and estimation. A further handicap was the sharp diminution in the yield of dimethylpolyene obtained in the reduction, as n increased above 5. Condensation of the bisbromomagnesium derivative of octa-4 : 6-dien-1-yn-3-ol with octatrienal gave the glycol (II; $a = 3$, $b = 2$), which on reduction at 0° or 15° and chromatographic isolation of the non-polar fraction yielded a product, the absorption spectrum of which (see Fig. 1) indicated the presence of the

* Part II, *J.*, 1954, 4006.

heptaene (I; $n = 7$) as the component mainly responsible for the long-wavelength absorption. The more accessible symmetrical glycol (II; $a = b = 3$) gave, on isolation of the non-polar fraction, a solution from which an apparently crystalline solid was isolated. Its spectrum (Fig. 1) indicates that the octaene (I; $n = 8$) must have been almost the only soluble light-absorbing substance present, although the intensity implies that the content of this was probably only *ca.* 20% (a roughly linear extrapolation from the lower polyenes being assumed). Alternatively the specimen may have been nearly pure, but so sparingly

FIG. 1. *Absorption spectra of dimethylpolyenes* (I) *in chloroform.*



– – – – From Bohlmann, *Chem. Ber.*, 1952, **85**, 386 (in benzene). (*a*) Prepd. from (II; $a = b = 3$). (*b*) Prepd. from (II; $a = 5$, $b = 1$).

(*N.B.* Except for $n = 3$ and $n = 6$, log E values are instrument readings, obtained with solutions of unknown concentration.)

soluble that much remained undissolved. At this point the belief that the non-polar substances responsible for the long-wavelength absorption were indeed the dimethylpolyenes was checked by condensing hex-2-en-5-yn-4-ol with dodeca-2 : 4 : 6 : 8 : 10-pentaenal : the glycol (II; $a = 5$, $b = 1$) was isolated chromatographically as a *ca.* 40% concentrate. On reduction it gave a non-polar fraction, the absorption bands of which agreed accurately with those observed for the reduction product of the diol (II; $a = b = 3$). The yield was much lower than from the symmetrical glycol.

For the preparation of the nonaene (I; $n = 9$), the glycol (II, $a = 5$, $b = 2$) was required. The Grignard reaction with dodeca-2 : 4 : 6 : 8 : 10-pentaenal was effected in tetrahydrofuran, and the desired product was obtained crystalline and essentially pure, although analytical data were, as usual with such polyenes, somewhat inaccurate. On reduction and isolation of the non-polar fraction a chloroform solution was obtained which

showed sharp absorption bands at 3810, 4010, and 4195 Å, together with more intense absorption at shorter wavelengths. A more polar fraction, eluted from deactivated alumina only by ether, showed bands at 3780, 4080, and 4360 Å; these fractions darkened considerably when shaken with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride solution, indicating the presence of conjugated carbonyl compounds. The curve published by Bohlmann (*loc. cit.*) for a product, obtained by treating docosa-2 : 4 : 6 : 8 : 12 : 14 : 16 : 18-octaene-10 : 11-diol (30 mg.) with phosphorus di-iodide, filtration through alumina, and recrystallisation from benzene–methanol, showed several maxima in benzene at up to 4360 and 4500 Å (see Fig. 1). This procedure might well give carbonyl compounds by pinacol-type dehydration, which would probably not be separated by the isolation procedure used; it is therefore not necessary to ascribe the longer-wavelength bands observed to the nonaene (I; $n = 9$). Our belief that the non-polar fractions obtained in the reduction of the diol (II; $a = 5$, $b = 2$) contained the nonaene (I; $n = 9$) depends upon analogy with the behaviour of lower members of the series of glycols (II), and upon the position of the absorption maxima in relation to those of the lower members of series (I), where constitution is securely established. The discrepancy with Bohlmann's results cannot, however, be explained by solvent effects, as benzene and chloroform give similar $\lambda_{max.}$ values in series (I) ($\Delta\lambda \not> 10$ Å).

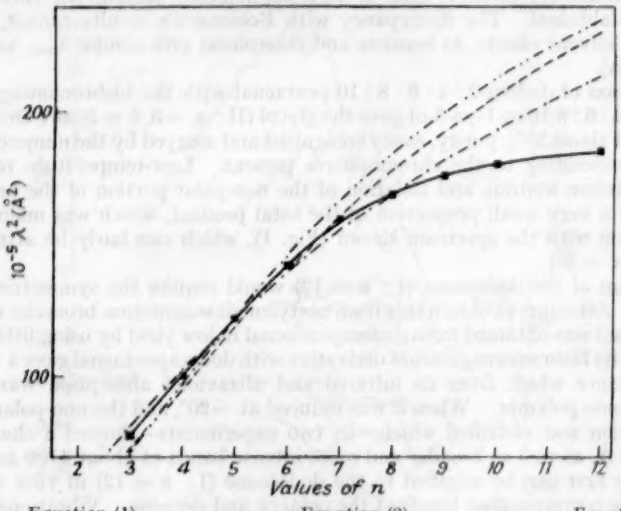
Condensation of dodeca-2 : 4 : 6 : 8 : 10-pentaenal with the bisbromomagnesium derivative of deca-4 : 6 : 8-trien-1-yn-3-ol gave the glycol (II; $a = 5$, $b = 3$) as a chromatographic concentrate of about 30% purity, easily recognised and assayed by the numerous absorption maxima corresponding to the chromophores present. Low-temperature reduction with lithium aluminium hydride and isolation of the non-polar portion of the benzene-soluble fraction (now a very small proportion of the total product, which was mainly polymeric) gave a solution with the spectrum shown (Fig. 1), which can fairly be attributed to the decaene (I; $n = 10$).

Preparation of the dodecaene (I; $n = 12$) would require the symmetrical glycol (II; $a = b = 5$). Attempts to obtain this from acetylenedi(magnesium bromide) failed; but an ethynylcarbinol was obtained from dodecapentaenal in low yield by using lithium acetylide. Treatment of its bisbromomagnesium derivative with dodecapentaenal gave a very sparingly soluble substance which from its infrared and ultraviolet absorption was the required glycol, plus some polymer. When it was reduced at −20°, and the non-polar fraction isolated, a solution was obtained which—in two experiments—showed a sharp absorption band at 4310 Å, as well as broader and more intense bands at about 4100 and 3870 Å (see Fig. 1). The first can be ascribed to the dodecaene (I; $n = 12$) in view of its position relative to the corresponding bands of the octaene and decaene. Vibrational sub-maxima of shorter wavelength should be of an intensity similar to, or smaller than, that of the longest-wavelength band [cf. results for the compounds (I; $n = 6$ or 8) or typical carotenoids], so the 4100 and 3870 Å bands must be due almost entirely to contaminants with a shorter polyene chromophore. For the same reason, the lower-wavelength bands of the other members of the series are, of course, distorted and increased in relative intensity where complete purification was impracticable.

Infrared results for the hydrocarbons (I; $n = 3$, 4, and 5) revealed in each case bands at 2900 cm.$^{-1}$, etc., and at 1380 and 1450 cm.$^{-1}$, attributable to the terminal methyl groups, and at 3000 cm.$^{-1}$ (olefinic C–H stretching). In the C=C stretching region, the strongest band was almost constant in position at 1640 cm.$^{-1}$, with weaker satellites at 1855, 1788, 1755, and 1672 cm.$^{-1}$ ($n = 3$), and 1875, 1817, 1722, and 1679 cm.$^{-1}$ ($n = 4$); the pentaene (I; $n = 5$) was insufficiently soluble for detection of such weak bands. The three polyenes differed somewhat in the olefinic C–H bending region, where the triene showed a sharp, intense band at 992 cm.$^{-1}$ and weaker bands at 958 and 916 cm.$^{-1}$; the tetraene showed a broad and strong band at 985 cm.$^{-1}$, another of comparable but lower intensity at 925 cm.$^{-1}$, and a sharp weak band at 940 cm.$^{-1}$; and the pentaene showed a strong, broad, complex band at 996 cm.$^{-1}$ with a relatively weak band at 926 cm.$^{-1}$. None absorbed at 660—750 cm.$^{-1}$, where *cis*-ethylenes have strong or medium absorption bands. The overall similarity of the spectra was unmistakable, and hydroxylic and carbonyl-containing contaminants were clearly absent.

Discussion.—The ultraviolet absorption spectra of the hydrocarbons (I), the main object of this work, are illustrated in Fig. 1. The octaene (I; $n = 8$) is important as bridging the gap between the well-defined and relatively tractable members of the series where $n = 2$—6, and the higher polyenes which were handled entirely in solution. The spectra for the members (I; $n = 7$, 9, and 10) are sufficiently complete and similar to that of the octaene for reasonable confidence to be placed in their authenticity; but that of the dodecaene (I; $n = 12$) is not, and relies for the acceptance of its 4310-Å maximum entirely on the smooth curve relating n and $\lambda_{max.}$ for the longest-wavelength band (Fig. 2). This shows clearly the breakdown of the Lewis–Calvin equation $\lambda^2 = kn$ (*Chem. Rev.*, 1939, **25**, 237) for polyenes (I) where $n > 6$. Series (I) converges much more sharply than the isoprenoid series $[CH{=}CMe{\cdot}CH{=}CH]_{\frac{1}{2}n}$ illustrated by the results of Karrer *et al.* (see Karrer and Eugster, *Helv. Chim. Acta*, 1951, **34**, 1805); one might estimate limiting wavelengths of 4500 and 6300 Å respectively in $CHCl_3$, or perhaps 4400 and 5900 Å in light petroleum.

FIG. 2. *Lewis–Calvin plot for longest-wavelength bands.*



— · · — · · Equation (1). — · — · — Equation (2). - - - - - - Equation (3).
———— Experimental values.

Three equations have recently been deduced theoretically for differences in energy levels of conjugated polyenes, and hence electronic absorption spectra, as a function of the chain length. They are (n = number of double bonds):

$$\lambda = a\{1 - b \cos [\pi/(n - 1)]\}^{-0.5} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(W. Kuhn, *Helv. Chim. Acta*, 1948, **31**, 1780) where a and b are parameters, calculated to be $1{\cdot}57 \times 10^3$ and 0·922 respectively;

$$\lambda = 1{\cdot}23 \times 10^{-4}/[18{\cdot}8(2n + 1)^{-1} + V_0(1 - \tfrac{1}{2}n^{-1})] \quad . \quad . \quad . \quad . \quad (2)$$

(H. Kuhn, *J. Chem. Phys.*, 1949, **17**, 1198), where V_0 is the only parameter, taken as 2·0; and

$$\lambda = D(1 - a^{2n-2}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(Dewar, *J.*, 1952, 3544), where D and a are treated as parameters, and assigned values of 6352 and $2^{\frac{1}{2}}$ respectively.

Each author has claimed good agreement with "experimental values." It is difficult to discuss the (very impressive) agreement between equation (1) and 18 polyenes chosen to

represent the latter, since these are not specified; four different empirical corrections were made to n, to allow for the effects of various end groups. Both H. Kuhn and Dewar (*locc. cit.*) assumed that the position of the absoprtion maximum was determined by the length of the polyene chain, and they neglected other environmental factors, *e.g.*, the numbers of alkyl substituents on the chromophore and of exocyclic double bonds (Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72), and the presence of non-coplanar trimethyl*cyclo*hexenyl groupings (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Oroshnik, Karmas, and Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 295) or of imperfectly insulated non-conjugated ethylenic linkages (Braude, *J.*, 1949, 1902). These factors, however, are not negligible; indeed, beyond a certain chain-length the positions of the absorption maxima of a polyene depend more upon the degree of substitution than upon

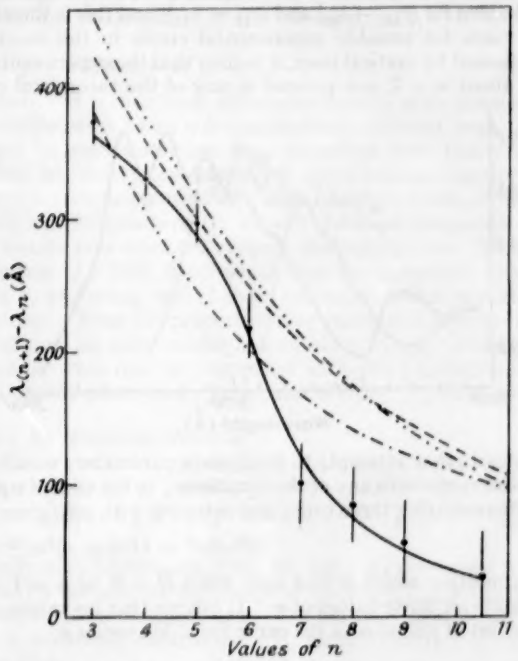


FIG. 3.

— · · — · · Equation (1).
— · — · — Equation (2).
– – – – – – Equation (3).
———— Experimental values.

the number of conjugated linkages. This approximation has resulted in a systematic error, in that both authors have chosen simple examples among the lower polyenes, but (of necessity) complex, highly alkylated examples of higher polyenes. Variations in the spectra of polyenes which differ in the respects indicated allow a considerable amount of freedom in the selection of experimental values to suit a given theoretical expression. In one case the arithmetical latitude has been increased through an error in the literature; Dewar (*loc. cit.*) used a number of wavelengths from a table by Karrer and Eugster (*loc. cit.*), but rejected that (4100 Å) given for dihydro-β-carotene in favour of another for the same substance (4200 Å; Braude, *Ann. Rep.*, 1945, **42**, 105) in better agreement with the calculated value of 4220 Å. Braude's value is, however, a mis-reading of the curve published by Karrer and Rüeger (*Helv. Chim. Acta*, 1940, **23**, 955), and later quoted correctly by Karrer and Eugster (*loc. cit.*).

An adequate experimental test of these theoretical equations clearly requires the examination of comparable substances under similar conditions; we believe that series (I) is the best yet available for this purpose. We have chosen, in Fig. 1, to plot the longest-wavelength band. This has the practical advantage of being the sharpest and most easily

distinguished, and the theoretical advantage that it must represent the zero–zero transition as regards the main vibrational processes in the newly excited molecule and therefore measures directly the energy difference in question. The other bands are spaced at a constant value of about 1450 cm.$^{-1}$, which does not vary significantly between the triene (I; $n = 3$) and the octaene (I; $n = 8$); this spacing, characteristic for polyenes, is in fact complex, being the result of two superimposed intervals of 1570 and 1230 cm.$^{-1}$ according to Hausser, R. Kuhn, and Seitz (*Z. phys. Chem.*, 1935, *B*, **29**, 391). H. Kuhn and Dewar (*locc. cit.*) have considered the second vibrational band, which is usually (but see Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 5227) the most intense.

It is possible to plot λ or λ^2 against n directly; then all three theoretical curves resemble qualitatively that of the experimental results. A more searching test is given by the differential curve, in which $(\lambda_{n+1} - \lambda_n)$ is plotted against n (Fig. 3); an average value only is known for $(\lambda_{11} - \lambda_{10})$ and $(\lambda_{12} - \lambda_{11})$, and this is therefore shown. Even when allowance is made for possible experimental errors in the exact locations of absorption maxima, indicated by vertical lines, it is clear that the experimental results require a point of inflexion at about $n = 7$, not present in any of the theoretical curves. This qualitative difference

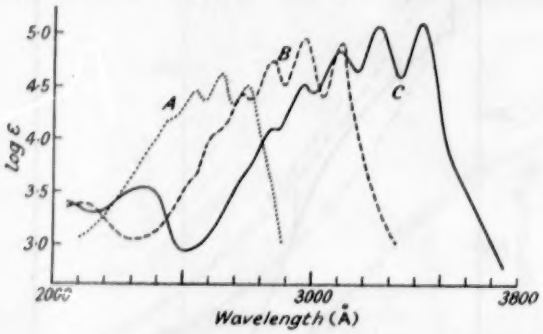


FIG. 4.
Absorption spectra of dimethylpolyenes (I) in hexane.
A, $n = 3$; *B*, $n = 4$; *C*, $n = 5$.

suggests that attempts to recalculate parameters would not give values consistent over the entire range with any of the equations; in the case of equation (3) this can be demonstrated. Differentiating three times and equating with zero gives:

$$d^3\lambda/dn^3 = 8D(\log_e a)^3 a^{-2n-2} = 0$$

a condition which is met only when $D = 0$, or $a = 1$, which substitutions lead to absurd results for finite values of n. It follows that no values of a and D can be found that permit a point of inflexion in the curve for $d\lambda/dn$ *versus* n.

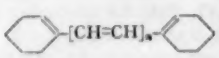
TABLE 1. *Absorption maxima of polyene series.*

n	(III) (hexane, etc.[a])		(I) (hexane)		(I) ($CHCl_3$)		(IV)	
	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
3	2675	56[b]	2745	30·2	2790	33·4[g]	2810	35[e]
4	3040	?[c]	3100	76·5	3165	?[h]		
5	3343	118[d]	3410	122	3495	?[i]		
6	—	—	—	—	3800	146·5		
7	3900	?[d]	—	—	4010	—		
8	—	—	—	—	4110	—	4260	132[f]

[a] In hexane, heptane, or *iso*octane. [b] Woods and Schwartzman, *J. Amer. Chem. Soc.*, 1948, **70**, 3394. [c] *Idem*, *ibid.*, 1949, **71**, 1396. [d] Mebane, *loc. cit.* [e] In EtOH. Burkhardt and Hindley, *J.*, 1938, 987. [f] In ether. Bohlmann, *Chem. Ber.*, 1951, **84**, 545. [g] $\lambda_{max.}$ 2745 Å, ε 30,200 in hexane. [h] $\lambda_{max.}$ 3100, ε 76,500 in hexane. [i] $\lambda_{max.}$ 3420, ε 122,000 in hexane.

Our values for series (I) (longest-wavelength band only) are tabulated (Table 1) for comparison with data recorded for series (III) and (IV), and accurate curves for the members (I; $n = 3$—5) in hexane are shown in Fig. 4. The tabulated results show a close similarity between series (I) and (III), but series (IV) must converge to a somewhat longer limiting wavelength. It should be noted that the value for the heptaene (III; $n = 7$) refers to a

mixture of geometrical isomers and is thus not exactly comparable with other data for series (I) and (III).

(III) $H\cdot[CH{=}CH]_n\cdot H$  (IV)

The availability of accurate intensity data for the hydrocarbons (I; $n = 3$—**6**) has permitted the calculation of oscillator strength values, using the equation

$$f = 4{\cdot}31 \times 10^{-9} \int \varepsilon d\bar{\nu}$$

(Maccoll, *Quart. Rev.*, 1947, **1**, 46). In Table 2 these are given alongside the corresponding experimental values for the di-*tert.*-butylpoly-ynes and Bayliss's theoretical predictions (*ibid.*, 1952, **6**, 319). Bayliss quoted the consequence of the free-electron approximation for polyenes as

$$f = 0{\cdot}134(n + 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where n is the number of double bonds. It is clear that, although the order of magnitude is correctly predicted, the true relation between f and n is qualitatively different from that implied by equation (**4**). Attempts to use carotenoids for comparison with theoretical relations are particularly misleading for absorption *intensities*, since non-coplanarity of terminal 2 : 2 : 6-trimethyl*cyclo*hexenyl groupings introduces large negative errors, evident when the values for vitamin A (1·05) and the pentaene (I; $n = 5$) (**1·66**) are compared.

In contrast, the experimental results now reported support the very simple chromophore-area theory proposed by Braude (*J.*, 1950, 379), which requires essentially that f should show a linear increase with n, neglecting end-of-chain anomalies which would be most prominent with the lower polyenes. Even the proportionality constant is near to that derived from these geometrical considerations, approaching a value given by $\varepsilon_{max.} = 25{,}000n$ for the two longest-wavelength bands; this may be compared with the constant value of $72{,}000n$ approached by the dimethylpoly-ynes (Cook, Jones, and Whiting, *J.*, 1952, 2883)

TABLE 2. *Oscillator strengths.*

	Dimethylpolyenes		Di-*tert.*-butyl-			Dimethylpolyenes		Di-*tert.*-butyl-	
n	calc.	exp.	poly-ynes	Ratio	n	calc.	exp.	poly-ynes	Ratio
3	0·94	0·74	2·08	2·81	5	1·47	1·66	4·10	2·48
4	1·21	1·11	2·99	2·69	6	1·74	2·17	5·15	2·37

or *ca.* $85{,}000n$ for the di-*tert.*-butylpoly-ynes (Bohlmann, 1953, **86**, 63). In agreement with this theory also is the consistent ratio for the polyene and the poly-yne series, the downward trend presumably representing the diminution of end-effects. The limiting value would be of considerable interest, if it could be accurately determined; H. Kuhn's theoretical value of 2·66 (*loc. cit.*) seems definitely too high.

EXPERIMENTAL

Ultraviolet absorption spectra were obtained with a Unicam SP 500 or Beckman DU spectrophotometer, with 95% EtOH as solvent unless otherwise stated. Infrared absorption spectra were measured with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics. M. p.s were determined on a Kofler block and are corrected. Light petroleum refers to the fraction of b. p. 40—60°, alumina to " Grade H " (Peter Spence, Ltd.), and deactivation implies treatment with 5% (by wt.) of 10% acetic acid. Reactions involving the use of lithium aluminium hydride or Grignard reagents were carried out in purified dry nitrogen, and whenever compounds with more than four conjugated linkages were handled solvents were redistilled in nitrogen before use and air was excluded as far as possible in evaporation, chromatography, and crystallisation; ether, benzene, etc., were usually evaporated at or below room temperature.

Sorbaldehyde and octa-2 : 4 : 6-trienal were prepared by the method of R. Kuhn *et al.* (*Ber.*, 1930, **63**, 2164; 1936, **69**, 98), whose yields were approximately reproduced. The latter aldehyde was also made by Kuhn and Grundmann's technique (*Ber.*, 1937, **70**, 1318), but then considerable quantities of dihydro-*o*-tolualdehyde, not mentioned in this paper, were formed, and the yield of the trienal was much lower than claimed. The use of very pure piperidine (Davies

and McGee, *J.*, 1950, 678) gave rather higher yields, and when the quantity of piperidine acetate was trebled the yield reached two-fifths of that reported. Schmitt and Overmeit's method (*Annalen*, 1941, **547**, 285) for preparing dodeca-2 : 4 : 6 : 8 : 10-pentaenal failed completely in our hands, violent reaction supervening. Blout and Fields (*loc. cit.*) described similar experiences with these self-condensation reactions, which are possibly very sensitive to impurities, present in piperidine and capable of inhibition or promotion of the catalyst (cf. R. Kuhn, *loc. cit.*).

Octa-4 : 6-dien-1-yn-3-ol.—A rapid stream of purified acetylene was passed into a stirred solution of lithamide (from 3·72 g. of lithium) in liquid ammonia (500 c.c.), contained in a vacuum-flask, until the formation of lithium acetylide was complete. A solution of sorbaldehyde (30 g.) in ether (100 c.c.) was added during 45 min. with slow passage of acetylene. The acetylene was replaced by nitrogen, and stirring continued for 1 hr. After decomposition with ammonium chloride (30 g.) and stirring for 30 min. the mixture was transferred to a beaker with the aid of ether (300 c.c.), covered with Cellophane, and protected from light. When all the ammonia had evaporated the residue was extracted with ether and the extracts were dried at 0° in the presence of quinol. Evaporation and distillation gave the *alcohol* (29·9 g., 79%), b. p. 50°/0·1 mm., n_D^{15} 1·5180 (Heilbron, Jones, and McCombie, *J.*, 1944, 134, give b. p. 71—4°/0·5 mm., n_D^{20} 1·5126).

Deca-4 : 6 : 8-trien-1-yn-3-ol.—This was prepared as above, from lithium (0·5 g.) in liquid ammonia (75 c.c.) and octa-2 : 4 : 6-trienal (4·0 g.) in ether (50 c.c.). Evaporation of the extract and crystallisation from light petroleum (b. p. 60—80°) gave the alcohol (3·5 g., 73%), m. p. 73° (Heilbron *et al.*, *loc. cit.*, give m. p. 73—74°).

Tetradeca-4 : 6 : 8 : 10 : 12-pentaen-1-yn-3-ol.—This was prepared as above from lithium (0·3 g.) in liquid ammonia (150 c.c.) and dodeca-2 : 4 : 6 : 8 : 10-pentaenal (1·0 g.) in tetrahydrofuran (75 c.c.). Crystallisation of the crude product from benzene–light petroleum gave the alcohol (0·8 g.). Light-absorption measurements indicated *ca.* 60% purity. A portion (0·12 g.) was chromatographed on alumina (50 g.). Elution with ether and crystallisation from light petroleum (b. p. 80—100°) gave fine yellow needles contaminated with amorphous polymer (50 mg.), decomp. above 100°. Light absorption : max., 3140, 3290, 3460 Å (ε 50,000, 71,500, 73,000); hence purity *ca.* 70%.

Dodeca-2 : 4 : 10-trien-7-yne-6 : 9-diol.—To a stirred solution of ethylmagnesium bromide (from 3·3 g. of magnesium) in benzene (250 c.c.) at 0° a solution of hex-4-en-1-yn-3-ol (Heilbron, Jones, and Weedon, *J.*, 1945, 81) (6·2 g.) in benzene (6 c.c.) was added and the mixture was stirred at 20° for 4 hr. After cooling to 0° a solution of sorbaldehyde (6 g.; freshly distilled) in benzene (6 c.c.) was added dropwise and the yellow solution was stirred at 20° for 14 hr. The Grignard complex was decomposed with saturated ammonium chloride solution. Isolation with ether and removal of the solvents under nitrogen gave a crude product which was chromatographed on alumina (120 g.; deactivated). Evaporation of the ether eluate gave an oil (3·1 g.) which on treatment with ether (2 c.c.) at 0° slowly crystallised, to give the *glycol* (2·5 g., 20%), obtained as needles, m. p. 80°, from benzene (Found : C, 74·6; H, 8·4. $C_{12}H_{16}O_2$ requires C, 74·9; H, 8·4%). Light absorption : max., 2300 Å (ε 28,000).

Hexadeca-2 : 4 : 6 : 12 : 14-pentaen-9-yne-8 : 11-diol.—To a stirred solution of ethylmagnesium bromide (from 3·0 g. of magnesium) in tetrahydrofuran (60 c.c.) at 0° a solution of octa-4 : 6-dien-1-yn-3-ol (7·1 g.) in tetrahydrofuran was added and the mixture was stirred at 20° for 2 hr. After cooling to 0° a solution of octa-2 : 4 : 6-trienal (7·1 g.) in tetrahydrofuran (40 c.c.) was added dropwise and the resulting red solution was stirred at 20° for 2 hr. After cooling to 0° the Grignard complex was decomposed with saturated ammonium chloride solution, and isolation with ether gave a red gum (13 g.) which was chromatographed in alumina (200 g.; deactivated). Evaporation of the ether eluate and crystallisation from di*iso*propyl ether–pentane gave the *glycol* (3·7 g., 26%) as needles, m. p. 114—116° (Found : C, 77·7; H, 8·15. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·25%). Light absorption : max., 2305, 2690, 2790 Å (ε 33,800, 56,000, 45,000); infl. 2605 Å (ε 42,000).

Hydrogenation. The glycol (0·11 g.) in 95% ethanol (23 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete : 70 c.c. were taken up at 26°/760 mm., corresponding to 7·0 mols.

Octadeca-2 : 4 : 6 : 8 : 10 : 16-hexaen-13-yne-12 : 15-diol.—To a solution of ethylmagnesium bromide (from 0·5 g. of magnesium) in tetrahydrofuran (25 c.c.) at 0° a solution of hex-4-en-1-yn-3-ol (0·9 g.) in tetrahydrofuran was added and the mixture was stirred at 20° for 5 hr. After cooling to 0° a solution of dodeca-2 : 4 : 6 : 8 : 10-pentaenal (1·7 g.) in tetrahydrofuran (75 c.c.) was added and stirring at 20° was continued for 14 hr. Decomposition as above and isolation with ether gave a yellow solid, which was chromatographed on alumina (100 g.; deactivated).

Elution with benzene removed unchanged dodecapentaenal (0·3 g.), and elution with ether then gave a glycol fraction (0·4 g.), about 40% pure [max., 3020, 3140, 3300, 3460 Å (ε 16,800, 27,200 38,000, 37,000)].

Docosa-2 : 4 : 6 : 8 : 10 : 16 : 18-heptaen-13-yne-12 : 15-diol, etc.—The C_{20} diol was prepared as above, by using ethylmagnesium bromide (from 1·4 g. of magnesium), octa-4 : 6-dien-1-yn-3-ol (3·6 g.), and dodeca-2 : 4 : 6 : 8 : 10-pentaenal (5·0 g.). Isolation of the crude product with ether and repeated crystallisation from benzene gave the glycol (1·3 g.) as a pale yellow solid, decomp. >120° (Found : C, 77·7; H, 7·95. Calc. for $C_{20}H_{24}O_2$: C, 81·05; H, 8·15%), evidently about 80% pure [max., 2300, 3030, 3150, 3300, 3470 Å (ε 23,400, 25,200, 49,300, 76,000, 73,500)].

Dodocosa-2 : 4 : 6 : 8 : 10 : 16 : 18 : 20-octaen-13-yne-12 : 15-diol was prepared as above, by using ethylmagnesium bromide (from 0·4 g. of magnesium), deca-4 : 6 : 8-trien-1-yn-3-ol (1·3 g.), and dodeca-2 : 4 : 6 : 8 : 10-pentaenal (1·0 g.). Isolation of the crude product with ether gave a dark brown solid, which was chromatographed on alumina (50 g.; deactivated). Elution of the glycol fraction with ether gave a gum (0·3 g.) for which light-absorption data indicate *ca.* 30% purity, the rest of the material being mainly polymeric [max. 2580, 2660, 2770, 3020, 3160, 3280, 3460 Å (ε 15,500, 18,500, 17,200, 21,200, 26,700, 32,000, 32,000)].

Hexadocosa-2 : 4 : 6 : 8 : 10 : 16 : 18 : 20 : 22 : 24-decaen-13-yne-12 : 15-diol was prepared as above, from ethylmagnesium bromide (from 0·16 g. of magnesium), tetradeca-4 : 6 : 8 : 10 : 12-pentaen-1-yn-3-ol (0·6 g., *ca.* 60% pure), and dodeca-2 : 4 : 6 : 8 : 10-pentaenal (0·6 g.) with a reaction period of 2 hr. at room temperature. Isolation with ether gave an orange solid which on extraction with hot benzene gave unchanged dodecapentaenal, m. p. 160—163°, $\lambda_{max.}$ 3780 Å (ε 50,000). The residue on repeated crystallisation from ethyl acetate–light petroleum gave the glycol (200 mg.) for which light-absorption data indicate *ca.* 60% purity [max. 3070, 3200, 3360, 3520 Å (ε 39,400, 70,500, 104,000, 112,000)].

Hexa-2 : 4-diene.—Hex-3-yne-2 : 5-diol (7·0 g.) (Iositch, *Bull. Soc. chim. France*, 1904, **32**, 553) in ether (*ca.* 30 c.c.) was added to lithium aluminium hydride (7·0 g.) in ether (200 c.c.), and the mixture was heated under reflux for 6 hr. Cautious addition of water and dilute sulphuric acid gave an ether layer which was dried and concentrated through a short Fenske column to about 2 c.c. *cyclo*Hexane (4 c.c.) was added, and the liquid was distilled at atmospheric pressure to a bath-temperature of 100°. Hexa-2 : 4-diene was estimated spectroscopically in the distillate (cf. Booker, Evans, and Gillam, *J.*, 1940, 1453); the yield was 11%. Separate portions were treated with bromine, giving 2 : 3 : 4 : 5-tetrabromohexane, m. p. 180° (Reif, *Ber.*, 1908, **41**, 2744, gives m. p. 180°), and with maleic anhydride, giving 3 : 6-dimethyl-1 : 2 : 3 : 6-tetrahydrophthalic anhydride, m. p. 95—96° (Diels and Alder, *Annalen*, 1929, **470**, 102, give m. p. 96°).

Octa-2 : 4 : 6-triene.—Oct-6-en-3-yne-2 : 5-diol (4·0 g.), lithium aluminium hydride (3·2 g.), and ether (150 c.c.) were heated under reflux for 5 hr. Addition of aqueous tartaric acid and evaporation of the dried ether layer gave a residue which was extracted with light petroleum (b. p. 30—40°), which was then evaporated. Crystallisation of the residue twice from methanol gave octa-2 : 4 : 6-triene (1·0 g., 32%) as plates, m. p. 50° (slight decomp.) (Kuhn and Grundmann, *loc. cit.*, give m. p. 52°). Isolation of the more polar fraction from the aqueous phase and the petrol-insoluble residue, and distillation, gave *octa-4 : 6-diene-2 : 3-diol* (1·3 g., 32%), b. p. 100—105°/10^{-3} mm., n_D^{17} 1·5150 (Found : C, 67·65; H, 9·9. Calc. for $C_8H_{14}O_2$: C, 67·6, H, 9·95%). Light absorption : max. 2290 Å (ε 24,400) [Ahmad, Sondheimer, Weedon, and Woods, *loc. cit.*, give b. p. 80° (bath-temp.)/10^{-4} mm., n_D^{20} 1·5100, $\lambda_{max.}$ 2290 Å (ε = 25,500)]. Quantitative periodate oxidation by Jackson's method ("Organic Reactions," Vol. II, Wiley, New York, 1944, p. 341) indicated a vicinal glycol content of 95%; on a larger scale (0·2 g.), periodate oxidation, steam-distillation, conversion into 2 : 4-dinitrophenylhydrazones, separation by chromatography, and fractional crystallisation gave the derivatives of acetaldehyde (0·1 g., 35%), m. p. and mixed m. p. 167°, and sorbaldehyde (0·15 g., 40%), m. p. and mixed m. p. 192°.

Deca-2 : 4 : 6 : 8-tetraene.—Deca-2 : 8-dien-5-yne-4 : 7-diol (Heilbron, Jones, and Raphael, *J.*, 1943, 268) (4·7 g.), lithium aluminium hydride (4·5 g.), and ether (200 c.c.) were heated under reflux for 18 hr. and the product was isolated with ether and extracted with light petroleum. Evaporation, sublimation at 60—70° (bath-temp.)/10^{-1} mm., and crystallisation from ethanol gave the hydrocarbon (0·95 g., 25%), as needles, m. p. 115° (decomp.) [Kuhn and Grundmann, *loc. cit.*, give m. p. 125° (sealed tube)].

Dodeca-2 : 4 : 6 : 8 : 10-pentaene.—The preparation was carried out as above from dodeca-2 : 4 : 10-trien-7-yne-6 : 9-diol (1·25 g.) and lithium aluminium hydride (1·0 g.) with a reaction period of 24 hr. Evaporation of the light petroleum (b. p. 60—80°) extracts gave a solid (0·4 g.). Sublimation of a portion (0·1 g.) at 60—70° (bath-temp.)/10^{-3} mm. and repeated crystallisation from ethanol gave the hydrocarbon (0·05 g., 15%) as minute cream leaflets, m. p. 150° (decomp.),

which rapidly polymerised (Bohlmann, *loc. cit.*, gives m. p. 155°) (Found: C, 88·6; H, 10·0. Calc. for $C_{12}H_{16}$: C, 89·95; H, 10·05%).

Tetradeca-2 : 4 : 6 : 8 : 10 : 12-hexaene.—This was prepared as above from tetradeca-2 : 4 : 10 : 12-tetraen-7-yne-6 : 9-diol (Heilbron, Jones, and Raphael, *loc. cit.*, 1944) (2·5 g.) in tetrahydrofuran (50 c.c.), and lithium aluminium hydride (2·5 g.) in ether (200 c.c.), with a reaction period of 4 hr. at 20°. The residue after evaporation of the ethereal extracts was extracted with benzene and the extracts were filtered through alumina. Evaporation of the benzene gave a solid (1 g.). Sublimation of a portion (0·4 g.) at 120° (bath-temp.)/10^{-5} mm. and crystallisation from ethanol gave the hydrocarbon (0·025 g.) as pale yellow plates, m. p. *ca.* 200° (decomp.) [Kuhn and Grundmann, *loc. cit.*, give m. p. 205° (evacuated tube)].

Hexadeca-2 : 4 : 6 : 8 : 10 : 12 : 14-heptaene.—The preparation was carried out as above, from hexadeca-2 : 4 : 10 : 12 : 14-pentaen-7-yne-6 : 9-diol (2·0 g.) in tetrahydrofuran (100 c.c.), and lithium aluminium hydride (2·0 g.), with a reaction period of 4 hr. at 0°, the solution becoming deep green. The residue after evaporation of the ethereal extracts was extracted with benzene, and the extract chromatographed on alumina. The benzene eluate was evaporated and the residue taken up in chloroform, to give a concentrate of the hydrocarbon ($\lambda_{max.}$ 3605, 3800, 4010 Å in $CHCl_3$). A second experiment gave a concentrate with max. at 3610, 3820, and 4020 Å.

Octadeca-2 : 4 : 6 : 8 : 10 : 12 : 14 : 16-octaene.—(*a*) The preparation was carried out as above, from octadeca-2 : 4 : 6 : 12 : 14 : 16-hexaen-9-yne-8 : 10-diol (Heilbron, Jones, and Raphael, *loc. cit.*, 1944) (0·4 g.) in tetrahydrofuran (25 c.c.), and lithium aluminium hydride (0·4 g.) in ether (60 c.c.), with a reaction period of 4 hr. at 20°. Evaporation of the ethereal extracts gave a residue which was warmed with ether, and the solution was passed through alumina (30 g.). Evaporation of the pale yellow filtrate and extraction with cold benzene (20 c.c.) gave a solution which was concentrated by blowing nitrogen over the surface; the hydrocarbon was precipitated as an apparently crystalline solid (3·7 mg.). Light-absorption data indicate that it was at least 20% pure [max. 3470, 3660, 3870, 4110 Å (ε 22,000, 31,000. 40,000, 35,200 in $CHCl_3$)].

(*b*) The preparation was carried out as above, from octadeca-2 : 4 : 6 : 8 : 10 : 16-hexaen-13-yne-12 : 15-diol (0·4 g., 40% pure) in tetrahydrofuran (50 c.c.), and lithium aluminium hydride (0·4 g.) in ether (50 c.c.), with a reaction period of 5 hr. Working up gave a hydrocarbon concentrate showing $\lambda_{max.}$ 3650, 3870, 4120 Å in $CHCl_3$.

Docosa-2 : 4 : 6 : 8 : 10 : 12 : 14 : 16 : 18-nonaene.—The preparation was carried out as above, using docosa-2 : 4 : 6 : 8 : 10 : 16 : 18-heptaen-13-yne-12 : 15-diol (1 g.; 80% pure) in tetrahydrofuran (50 c.c.), and lithium aluminium hydride (0·7 g.) in tetrahydrofuran (100 c.c.), with a reaction period of 1 hr. at −20°. The ethereal extracts were concentrated to small volume, benzene (80 c.c.) was added, and the solution was washed with water three times to remove tetrahydrofuran. The dried benzene solution was chromatographed on alumina (30 g.; deactivated). The benzene eluate was concentrated to half its volume and methanol (30 c.c.) was added. After concentration to 4 c.c., a further quantity of methanol (30 c.c.) was added and the solution was again concentrated to 4 c.c. Water (15 c.c.) was then added and the solution was extracted with hexane (10 c.c.). The hexane solution was evaporated nearly to dryness and the residue was taken up in chloroform. The solution showed light absorption with maxima at 3630, 3810, 4010 and 4195 Å. Elution of the more polar fractions with ether and evaporation nearly to dryness gave a yellow residue, $\lambda_{max.}$ 3780, 4080, 4300 Å in $CHCl_3$, which darkened when shaken in benzene with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride.

Dodocosa-2 : 4 : 6 : 8 : 10 : 12 : 14 : 16 : 18 : 20-decaene.—The preparation was carried out as above, from dodocosa-2 : 4 : 6 : 8 : 10 : 16 : 18 : 20-octaen-13-yne-12 : 15-diol (0·3 g., 30% pure) in tetrahydrofuran (20 c.c.), and lithium aluminium hydride (0·5 g.) in ether (60 c.c.), with a reaction period of 4 hr. at 20°. Evaporation of the ethereal extract, extraction of the residue with benzene, and chromatography on alumina (20 g.) gave a hydrocarbon fraction which on concentration and extraction with chloroform gave a solution showing light absorption with maxima at 3840, 4040, and 4250 Å.

Hexadocosa-2 : 4 : 6 : 8 : 10 : 12 : 14 : 16 : 18 : 20 : 22 : 24-dodecaene.—The preparation was carried out as above, from hexadocosa-2 : 4 : 6 : 8 : 10 : 16 : 18 : 20 : 22 : 24-decaen-13-yne-12 : 15-diol (0·2 g., 50% pure) in tetrahydrofuran (20 c.c.), and lithium aluminium hydride (0·2 g.) in tetrahydrofuran (25 c.c.), with a reaction period of 1 hr. at −20°. Evaporation of the tetrahydrofuran and ethereal extracts and extraction with ether, followed by chromatography on alumina (20 g.), gave a hydrocarbon fraction which on concentration and extraction with chloroform showed maxima at 3870, 4100, and 4310 Å. A second experiment gave a concentrate with maxima at 3850, 4120, and 4310 Å.

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Liquid Metals. Part III. The Influence of Oxide Films on the Surface Tension of Liquid Sodium.*

By C. C. ADDISON, W. E. ADDISON, and D. H. KERRIDGE.

[Reprint Order No. 6349.]

The drop-volume technique has been used to determine the changes in surface tension of liquid sodium which occur when dry air is introduced into the argon atmosphere surrounding the metal drops. At 180°, the surface tension decreases linearly with partial pressure of oxygen, from 194 to 186 dynes/cm. A minimum occurs at an oxygen partial pressure of 2×10^{-4} atm., after which the tension can increase to very high values. The tension minimum is related to the change from a soluble to an insoluble film of sodium oxide at the metal surface.

THE formation of oxide films at the metal surface represents the main source of error in surface-tension determinations on liquid metals, yet very little is known of the extent to which such films influence the tension. Taylor (A.E.R.E. Report M/R 1247; *J. Inst. Met.*, 1954—55, **83**, 143), using the maximum bubble pressure method and an argon atmosphere, observed that the surface tension of liquid sodium increased on addition of oxygen to the argon (by 21 dynes/cm. in the presence of 5% of oxygen); it was suggested that the high values of tension obtained by Poindexter and Kernaghan (*Phys. Rev.*, 1926, **23**, 820; see also Part II, *J.*, 1955, 2262) resulted from the presence of an oxide film, but there is no direct proof of this. According to Portevin and Bastien (*Compt. rend.*, 1936, **202**, 1072) the surface tension of pure liquid aluminium can be increased by a factor of two by oxidation of the surface. In contrast, Davis, Mack, and Bartell (*J. Phys. Chem.*, 1941, **45**, 846) observed that the surface tension of liquid gallium is reduced from 735 to 300 dynes/cm. at 30·5° on admission of air to the system, and an oxide film could be responsible for this change. Measurements on solid silver at a temperature just below its melting point also suggest a lowering of surface tension by oxide films (Buttner, Funk, and Udin, *ibid.*, 1952, **56**, 657).

Since the surface tension of fused metal oxides is normally much lower than that of the corresponding metals (see Bondi, *Chem. Rev.*, 1953, **52**, 417) the presence of oxide at the surface would be expected to lower the surface tension of the metal. Published data show no general agreement on this issue; this is considered to result from the dual role which oxide films can play. If the oxide is present in such small quantity that it will dissolve in the liquid metal, a soluble film will be formed which will lower surface tension to an extent which will depend on, *inter alia*, the solubility of the oxide. Continued formation of oxide beyond the solubility limit will give rise to an insoluble film; if the oxide concerned is cohesive in nature, it can act to some extent as a separate phase, and the apparent tension then represents the sum of the tension of the liquid metal and the tension in the separate cohesive film. As the quantity of oxide present is increased, the surface tension of a liquid metal may therefore pass through a minimum.

The purpose of the work described in this paper was to test this hypothesis in the case of liquid sodium. The solubility of sodium monoxide in the metal is very small [0·004 wt. % of Na_2O at 200°, Liquid Metals Handbook, NAVEXOS P-733 (Rev.), 2nd Edn., 1952, p. 114] but the cohesion of the oxides is high.

* Part II, *J.*, 1955, 2262.

Experimental

The drop-volume technique described in Part II was used. The pure argon atmosphere was contaminated with known amounts of dry air, and the resulting change in surface tension determined from the change in drop volume of sodium.

Contamination of the argon was carried out as follows. Argon–air mixtures of known composition (2—30% of air by volume) were prepared in a 5-l. aspirator, and kept under slight pressure by connecting the aspirator with a second elevated vessel containing water. The rate of flow of gas mixture was controlled by an Ermeto fine-control valve; the gas passed successively through a phosphoric oxide drying tube, a sintered glass plate which acted as dust filter, and a

Fig. 1.

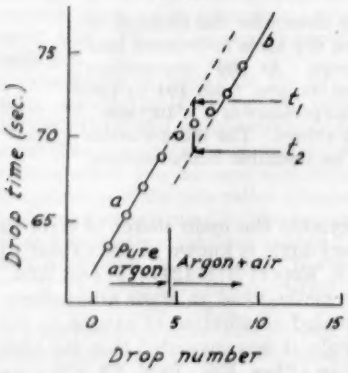


Fig. 2.

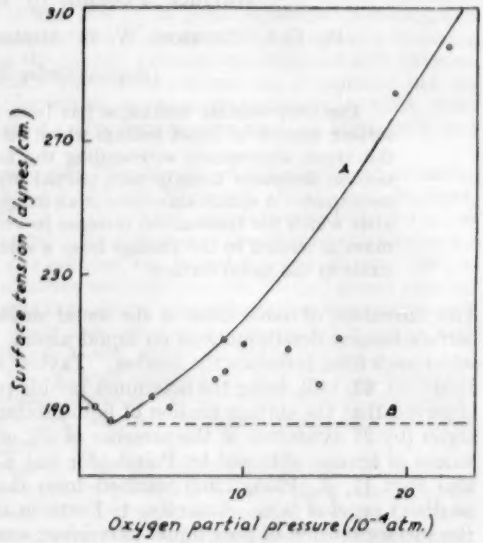
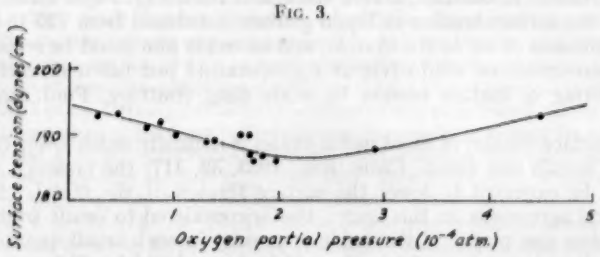


Fig. 3.



flow meter. It then entered the main argon stream at a position as near as possible to that at which the argon entered the drop-volume apparatus, so that its presence was rapidly reflected in change of behaviour of the metal drops. The main argon stream flowed at a rate near 1300 ml./min. throughout the experiment; the argon–air mixture flow rate was in the range 10—70 ml./min. (measured with an accuracy of 1 ml./min.) and from these quantities the oxygen partial pressures quoted in Figs. 2 and 3 were calculated.

In each determination, the sodium was allowed to flow from the pipette into a pure argon atmosphere until the flow rate was steady. Since the head of pressure in the pipette falls, steady flow is shown by a regular increase in drop time (line *a*, Fig. 1). When these conditions were achieved, contaminated argon was introduced; increase or decrease in surface tension is revealed by a corresponding increase or decrease in time of formation of the drops. The measurements shown in Fig. 1 are typical of those obtained on introduction of a very small

quantity of air into the argon stream. Since a short time is required for the oxygen content of the argon surrounding the orifice to reach its final value, drop times did not undergo full adjustment immediately, but within the period for 3—4 drops, the drop times moved from line *a* to a line *b* which is nearly parallel with *a*. Lines *a* and *b* are of course short sections from curves which are not parallel, and drop volumes were therefore calculated from drop times t_1 and t_2 determined as shown in Fig. 1. When the difference between t_1 and t_2 was considerable, tensions were calculated by using the usual equation $\gamma = mgF/r$. This was the case only with the most heavily contaminated surfaces, and for most experiments the variation in correction factor F was so small that the tension of the contaminated surface could be obtained with sufficient accuracy by using the simple relation $\gamma = \gamma_{Na}t_1/t_2$.

Results and Discussion

The variation in surface tension at 180° with oxygen partial pressure (over the low partial-pressure range) is shown in Fig. 3, from which it is at once apparent that the presence of oxygen at first causes lowering of the surface tension, but that slight surface contamination does not have any marked effect on the measured tension values. At an oxygen partial pressure of about 2×10^{-4} atm. the tension value passes through a minimum, and increases thereafter. When the quantity of oxygen was less than about 2×10^{-4} atm., the drops normally remained bright, whereas with higher oxygen partial pressures, films of undissolved oxide were visible. The appearance of undissolved oxide on the surface therefore broadly coincided with the minimum in the surface-tension curve; the initial decrease in tension from 194 to 186 dynes/cm. results from a soluble film of sodium oxide, and the fact that the decrease is only 8 dynes/cm. is a consequence of the very low solubility of sodium oxide. It is of interest that the tension value of 186 dynes/cm. at 180° obtained by the vertical plate technique (Part I, *J.*, 1954, 2861), in which the sodium surface is exposed for longer periods, agrees with the minimum value observed in these experiments (Fig. 3), so that the range of values for the tension of " pure " sodium obtained by the various techniques is also that for which sodium oxide can be responsible.

At oxygen partial pressures beyond the minimum in the tension curve, an insoluble oxide film is formed, and the cohesion in this film is responsible for the increase in the apparent surface tension. The behaviour of the drops under these conditions was erratic. When the oxide film remained unbroken throughout drop formation, maximum values of tension (representing the sum of the true sodium tension and the film cohesion) were obtained, and these conditions are represented by curve *A*, Fig. 2, which could be extended to tensions as high as 450 dynes/cm. Frequently, however, the film cracked, exposing clean sodium metal, and lower tension values were then obtained. According to the general hypothesis all values should lie between curve *A* (maximum film cohesion) and line *B* (no film cohesion); this was the case, and no values were obtained below line *B*. This interpretation is consistent with observations by Moyer and Ruggles (Knolls Atomic Power Laboratory Report KAPL-519, May 1951) who studied the optical properties of a liquid sodium surface by reflection of plane-polarised light from the surface. They found that small quantities of oxygen in a helium atmosphere dissolved in the liquid metal without change in the optical characteristics of the surface, but that addition of oxygen in excess of the solubility limit gave rise to clumps of oxide crystals, the space between the crystals being covered with a thin oxide film.

The results in Fig. 3 show that reaction between sodium and dry air is very slow, since sufficient oxygen was available at all times to give rise to heavy contamination of the drops. It is, indeed, only in such circumstances that measurements of the type shown in Fig. 3 are possible. Using a solid sodium surface, Moyer and Ruggles (*loc. cit.*) found that 10—15 days were required before reaction with traces of oxygen in a helium atmosphere was complete. Their observation that small amounts of nitrogen sensitised the surface so that the oxygen was taken up in less than a second is also of interest; nitrogen was present in the experiments described here, and may be responsible for some increase in reaction rate, but its catalytic activity at the liquid-metal surface appears to be much less than at the solid surface. The results serve to establish the general influence of oxygen on surface tension, but the Gibbs absorption isotherm cannot be applied to the falling

tension curve (Fig. 3) since equilibrium is not established under the conditions of these experiments. For this reason also, variation in the rate of drop formation (between 15 and 75 seconds per drop) had little effect on the tension values. Reaction at the surface is believed to follow the form

$$Na + O_2 \longrightarrow NaO_2 \xrightarrow{Na} Na_2O_2 \xrightarrow{Na} Na_2O$$

Although dissolved oxygen is no doubt present as sodium monoxide, an insoluble film may well contain sodium peroxide, since this compound is not readily wetted by sodium. The sodium–oxygen reaction is much more rapid in the presence of moisture; the decrease in tension with oxygen content is then likely to be more rapid than in Fig. 3, and the values may also depend to some extent on rate of drop formation. However, since systems to which the present measurements are relevant are scrupulously dried, this aspect was not further investigated.

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The Epimerisation of Sugars.

By J. K. N. JONES and W. H. NICHOLSON.

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De-esterification of the 2-*O*-toluene-*p*-sulphonyl or 2-*O*-methanesulphonyl derivatives of arabinose, xylose, and fucose converts them into ribose, lyxose, and talomethylose respectively. Similarly 3-*O*-methanesulphonyl-D-fructose is converted into D-psicose.

1 : 2-ANHYDRO-D-RIBOSE was required for a research project. We attempted to prepare this compound from 2-*O*-methanesulphonyl-D-arabinose by alkaline hydrolysis but obtained, instead, D-ribose in high yield. This led us to study the alkaline hydrolyses of the 2-*O*-toluene-*p*-sulphonyl and 3-*O*-methanesulphonyl derivatives of the methylpentose and ketose sugars respectively.

2-*O*-Methanesulphonyl-D-arabinose was prepared from methyl 2-*O*-methanesulphonyl-3 : 4-*O*-*iso*propylidene-β-D-arabinoside. We report new constants for this compound (cf. Overend and Stacey, *J.*, 1949, 1235). Crystalline 2-*O*-toluene-*p*-sulphonyl-D-xylose was prepared from methyl 3 : 5-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-αβ-D-xylofuranoside (cf. Percival and Zobrist, *J.*, 1952, 4308), and 2-*O*-toluene-*p*-sulphonyl-L-fucose was isolated after hydrolysis of methyl 3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-α-L-fucoside (Percival and Percival, *J.*, 1950, 690). All three of these glycosides were relatively stable to hydrolysis by acids, presumably owing to the 2-sulphonyloxy-substituent (cf. Richards, *Chem. and Ind.*, 1955, 228). 3-*O*-Methanesulphonyl-D-fructose was isolated as a syrup after acidic hydrolysis of 3-*O*-methanesulphonyl-1 : 2-4 : 5-di-*O*-*iso*propylidene-D-fructose.

In order to convert these carbohydrate sulphonic esters into the epimeric sugars they were dissolved in water and their solutions were titrated with 0·3N-barium hydroxide to a phenolphthalein end-point. The mixtures were then de-ionised with Amberlite resins, IR-120 and IR-4B, and concentrated to a syrup. The epimer from 2-*O*-toluene-*p*-sulphonyl-D-xylose contained lyxose, and also xylose and traces of sugars identified chromatographically as a keto-D-*threo*pentose and D-arabinose. This mixture was fractionated on a cellulose column and pure D-lyxose was isolated. L-Talomethylose was obtained in crystalline form from the mixture resulting when the toluene-*p*-sulphonyl group was eliminated from 2-*O*-toluene-*p*-sulphonyl-L-fucose. D-Ribose was obtained crystalline only after separation from a small amount of arabinose on a cellulose column.

D-Psicose resulting from the elimination of the methanesulphonyl group from 3-*O*-methanesulphonyl-D-fructose was obtained as a chromatographically pure syrup which was characterised as D-allosazone and as the crystalline di-*O*-*iso*propylidene derivative of D-psicose.

The mechanism of the formation of these epimeric sugars is not clear. They may be formed *via* a 1 : 2-anhydro-sugar or by direct inversion at $C_{(2)}$. However, alkaline hydrolysis of methyl 2-*O*-methanesulphonyl-3 : 4-*O*-*iso*propylidene-β-D-arabinoside yielded methyl 3 : 4-*O*-*iso*propylidene-β-D-arabinoside by elimination of the methanesulphonyl group without inversion (cf. *Adv. Carbohydrate Chem.*, 1953, **8**, 167) which by acid hydrolysis afforded methyl β-D-arabinoside. This indicates that the second mechanism may not be operative in the transformations described above. The epimers are not formed by conversion of the sugars into an equilibrium mixture under the influence of a basic catalyst as they are produced in high yield. Fructose and fucose possess the same configuration of secondary alcohol groups as arabinose and may be considered as derivatives of this sugar. Anhydro-ring formation involving the reducing hydroxyl group of these sugars would result in the formation of ribose derivatives. If, then, the 1 : 2-anhydro-ring were opened in accordance with the Fürst–Plattner rule two axially oriented hydroxyl groups would result. This may explain the high yields of epimers obtained in this reaction.

While this work was in progress the conversion of 4-*O*-formyl-2-*O*-methanesulphonyl-D-arabinose into D-ribose was reported by Smith (*Chem. and Ind.*, 1955, 92).

Experimental

Concentrations were carried out under reduced pressure. Sugars were detected on chromatograms with the *p*-anisidine hydrochloride spray. The following solvents were used in chromatographic separations on Whatman No. 1 paper : (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (*b*) butan-1-ol–pyridine–water (10 : 3 : 3); (*c*) butan-1-ol–ethanol–water (4 : 1 : 2); and (*d*) ethyl acetate–acetic acid–water (9 : 2 : 2) (all v/v). Solutions were de-ionised with Amberlite resins IR-4B and IR-120.

2-O-*Methanesulphonyl*-D-*arabinose*.—Methyl 2-*O*-methanesulphonyl-3 : 4-*O*-*iso*propylidene-β-D-arabinoside (6·5 g.) {m. p. 140—141°, $[\alpha]_D^{24}$ −185° (*c*, 1·0 in $CHCl_3$); reported by Overend and Stacey (*loc. cit.*) to have m. p. 136·5—137·5°, $[\alpha]_D^{24}$ −333° (*c*, 0·045 in $CHCl_3$)} was boiled under reflux with 2N-sulphuric acid (244 c.c.) for 24 hr. The solution was very carefully neutralised with barium carbonate and filtered immediately through a Celite pad. The filtrate was evaporated to dryness under diminished pressure and the residue extracted with alcohol. The extract was filtered through charcoal and evaporated to a colourless syrup (4·4 g.), $[\alpha]_D^{24}$ −85° (*c*, 4·4 in H_2O), R_{RH} 1·2 (solvent *c*), R_{RH} 1·4, and R_F 0·58 (solvent *d*), showing one component only with the *p*-anisidine or silver nitrate reagent (R_{RH} is relative to rhamnose). The material reduced Fehling's solution.

D-*Ribose*.—2-*O*-Methanesulphonyl-D-arabinose (1·09 g.) in water (25 c.c.) was titrated slowly with saturated barium hydroxide solution to a phenolphthalein end-point. The solution was de-ionised and evaporated to dryness. The residual syrup, which was contaminated with a small amount of arabinose (detected chromatographically), was purified on a small cellulose column by elution with butan-1-ol half saturated with water. The eluate was evaporated to dryness, and the residue dissolved in water and filtered through charcoal. The filtrate was evaporated to dryness, and the residue on trituration with alcohol and seeding with authentic ribose crystallised, giving D-ribose (0·18 g.), $[\alpha]_D^{24}$ −22·8° (*c*, 1·8 in H_2O), m. p. 93—94°, mixed m. p. 90—91°.

D-*Ribose Toluene*-p-*sulphonhydrazone*.—D-Ribose (0·072 g.) in methanol (10 c.c.) was boiled under reflux with a solution of toluene-*p*-sulphonhydrazide (0·7 g.) in methanol (10 c.c.) for ½ hr. The solution was stored in the refrigerator for 24 hr. The crystalline residue was collected, washed with cold methanol and dried (0·122 g.; m. p. and mixed m. p. 174°).

2-O-*Methanesulphonyl*-3 : 4-O-iso*propylidene*-D-*arabinose*.—2-*O*-Methanesulphonyl-D-arabinose (1·0 g.) in acetone (50 c.c.) was shaken with anhydrous copper sulphate (5 g.) for 10 days. The course of the reaction was followed chromatographically, the product having R_{RH} 2·1 and R_F 0·86 (solvent *d*). The mixture was filtered, the filtrate concentrated to dryness, and the residue dissolved in ether. The ethereal solution was extracted with a little water, dried ($MgSO_4$), concentrated to a small volume, and placed in the refrigerator. The crystalline residue

was collected {0·250 g.; $[\alpha]_D^{24}$ −118° (*c*, 2·06 in acetone); m. p. 127—128°}. After recrystallisation from ether–acetone, it had m. p. 130—131°, not changed by further recrystallisation (Found: C, 40·1; H, 6·0; S, 11·7. Calc. for $C_9H_{16}O_7S$: C, 40·3; H, 6·0; S, 11·9%).

Methyl 3 : 4-O-iso*Propylidene*-β-D-*arabinoside*.—Methyl 2-*O*-methanesulphonyl-3 : 4-*O*-*iso*propylidene-β-D-arabinoside (5 g.) was heated in alcohol (200 c.c.) containing sodium hydroxide (0·75 g.) for 16 hr. The solution was filtered and the filtrate concentrated to dryness. The residue was extracted with light petroleum (b. p. 40—60°), and the extract filtered and concentrated to a syrup (1·9 g.), b. p. 100° (bath-temp.)/0·5 mm., n_D^{26} 1·4622, $[\alpha]_D^{20}$ −197° (*c*, 1·848 in $CHCl_3$) (Found: OMe, 14·0. Calc. for $C_9H_{16}O_5$: OMe, 15·2%).

Methyl β-D-*Arabinoside*.—Methyl 3 : 4-*O*-*iso*propylidene-β-D-arabinoside was dissolved in ether, acidified, and set aside for 16 hr.; crystals separated, having m. p. 167—168°, $[\alpha]_D^{22}$ −235° (*c*, 1·65 in MeOH) (Found: C, 44·1; H, 7·3; OMe, 18·9. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3; OMe, 18·9%).

2-O-*Toluene*-p-*sulphonyl*-D-*xylose*.—Methyl 3 : 5-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-αβ-D-xylofuranoside (11·3 g.) (Percival and Zobrist, *loc. cit.*) was dissolved in ethanol–water (1 : 1; 50 c.c.) containing concentrated hydrochloric acid (5 c.c.). The solution was heated on the boiling-water bath and the hydrolysis followed chromatographically (solvent *b*). After 5 hr. the solution contained a trace of xylose and two other components which moved at rates 1·6 and 2·06 relative to rhamnose. The faster-moving component was the major product. The solution was neutralised with barium carbonate, then filtered and the filtrate extracted exhaustively with chloroform. Concentration of the extract gave a crystalline residue (7·2 g.), easily soluble in methanol, ethanol, dioxan, and ethyl acetate, sparingly soluble in chloroform and ether. The product, 2-*O*-toluene-*p*-sulphonyl-D-xylose, recrystallised from ethyl acetate–chloroform, had m. p. 148°, $[\alpha]_D$ 14° (*c*, 0·5 in H_2O), and moved at twice the rate of rhamnose in solvent (*b*) (Found: C, 47·5; H, 5·3; S, 10·0. Calc. for $C_{13}H_{16}O_7S$: C, 47·3; H, 5·3; S, 10·5%).

Conversion of 2-O-*Toluene*-p-*sulphonyl*-D-*xylose into* D-*Lyxose*.—The toluene-*p*-sulphonyl derivative (0·91 g.) was dissolved in water, and 0·1N-sodium hydroxide (30 c.c.) added slowly at 40°. At this stage the solution was alkaline to phenolphthalein. After 15 min. the solution was acidified with acetic acid and de-ionised. The neutral effluent, $[\alpha]_D$ −6° (*c*, 2·7 in H_2O), was concentrated and examined chromatographically. The major component present was lyxose; a minor component was xylose; and unchanged starting material and small quantities of arabinose and ketothreopentose were also detected. The concentrate was fractionated on a column of cellulose with butan-1-ol half saturated with water as eluant. Concentration of the appropriate fractions of effluent from the column gave D-lyxose (0·4 g.) which slowly crystallised. Trituration with ethanol gave pure D-lyxose, m. p. and mixed m. p. 115°, $[\alpha]_D$ −14° (equil.).

Preparation of L-*Talomethylose* (with Mr. J. L. Thompson).—Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-α-L-fucoside (1 g.) was heated in 4N-hydrochloric acid (20 c.c.) on the water-bath for 3 hr. Paper chromatography (solvent *b*) then indicated complete hydrolysis, the mixture containing one component which moved, relative to rhamnose, at a rate of 2·1 (solvent *c*). The solution was neutralised with barium carbonate and filtered. The filtrate was titrated with 0·3N-barium hydroxide (10 c.c.) until a permanent pink colour was produced (phenolphthalein), then acidified with acetic acid, de-ionised, and concentrated. The syrupy residue (0·32 g.) contained talomethylose, which moved at 1·7 times the speed of rhamnose (solvent *b*) and traces of fucose (R_{RH} 0·7). On trituration with acetone the syrup crystallised. The crystals (0·22 g.) were collected and had m. p. and mixed m. p. 118—120° (Found: C, 44·1; H, 6·8. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%). The syrup remaining gave with methylphenylhydrazine solution a methylphenylhydrazone (0·092 g.), m. p. 181°.

Conversion of D-*Fructose into* D-*Psicose*.—3-*O*-Methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-fructose, m. p. 142° (1·62 g.) (3 : 4-di-*O*-acetyl derivative, m. p. 81°), was heated in 0·2N-sulphuric acid (11 c.c.) on the water bath for 30 min. Chromatography then indicated complete hydrolysis. The cooled solution was neutralised with barium carbonate and filtered and the filtrate titrated with 0·3N-sodium hydroxide (20 c.c.) until the solution remained alkaline for 10 min. The mixture was then acidified (acetic acid), de-ionised, and concentrated. The resulting syrup, examined chromatographically, was found to contain a ketose which moved at the same rate as psicose. A sample gave an osazone, m. p. 165° alone or mixed with D-allosazone. The residual syrup was shaken overnight with acetone (100 c.c.) and concentrated sulphuric acid (1 c.c.). The acid catalyst was then removed with anhydrous potassium carbonate, and the solution filtered. The filtrate was concentrated, dissolved in water, and extracted with light petroleum (b. p. 40—60°). The aqueous solution was extracted with

chloroform, and the extract dried and concentrated to a syrup which rapidly crystallised (0·61 g.), having m. p. and mixed m. p. 58° after recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 55·6; H, 7·3. $C_{12}H_{20}O_6$ requires C, 55·3; H, 7·7%).

We thank the Institute of Seaweed Research, Inveresk, Midlothian for a gift of L-fucose, the National Research Council of Canada for a grant which helped to defray part of the cost of this investigation, and Dr. R. B. Kelly for fruitful discussion.

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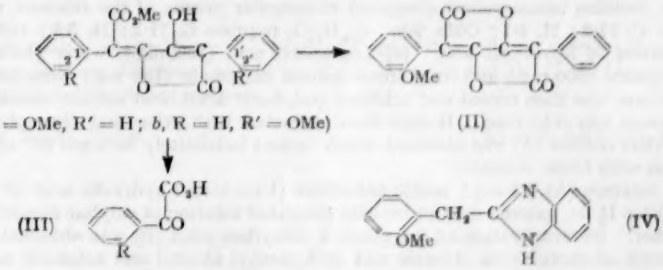
*Chemical Investigation of Indian Lichens. Part XIX.**
Lepraria: *Constitution of Leprapinic Acid.*

By O. P. MITTAL and T. R. SESHADRI.

[Reprint Order No. 6370.]

Two Indian lichens of the genus *Lepraria* have been examined. *L. flava* (Schreb) Ach. yielded pinastric acid, and *L. citrina* Schaer yielded a new lichen acid, leprapinic acid. Its constitution has been established as methyl 2-methoxypulvinate, the methoxyl group being located in the phenyl nucleus next to the ester group.

INDIAN lichens belonging to the genus *Lepraria* have not been studied before. They occur as deep yellow or orange powders on trees. Two of them have now been collected and examined. The first was obtained from the bark of pine trees on Kodaikanal hills in South India and was identified as *L. flava* (Schreb) Ach. by Mr. D. D. Awasthi of Lucknow University. Extraction with light petroleum yielded orange yellow crystals, identified as pinastric acid [*L. flava* Quercina was examined by Zopf (*Annalen*, 1905, **338**, 35) who reported the presence of calycin and calyciarin along with pinastric acid]. The second sample was collected from the bark of deodar trees in Simla and was identified by Dr. G. A. Llano of Washington University as *Lepraria citrina* Schaer. This yielded a light petroleum-soluble, golden-yellow compound, which is a new member of the pulvinic acid series and is named leprapinic acid [the simpler names, leprarin and lepraric acid, have been used for other substances (Zopf, *Annalen*, 1897, **295**, 257; Hesse, *J. prakt. Chem.*, 1898, **58**, 465)]. It has the formula $C_{18}H_{10}O_4(OMe)_2$. One methoxyl group is hydrolysed by alkali and hence is present in an ester group. The other is affected only by hydriodic acid and hence constitutes an ether group. The product of hydrolysis by alkali has a free carboxyl group and when refluxed with acetic anhydride yields a dilactone in the same way as does pulvinic acid. This dilactone was different from 4-methoxypulvinic dilactone (Asano and Kameda,



Ber., 1935, **68**, 1565). Though its melting point was very close to that of 3-methoxypulvinic dilactone (Asano and Huziwara, *J. Pharm. Soc. Japan*, 1939, **59**, 83), it gave a depression with an authentic sample. It should therefore be 2-methoxypulvinic dilactone

* Part XVIII, *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 403.

(II). This has been confirmed by degradation by alkaline potassium permanganate to *o*-methoxybenzoic and benzoic acid.

Leprapinic acid is therefore a methyl *o*-methoxypulvinate (I*a* or *b*). After oxidation with cold alkaline permanganate, evidence for the formation of two glyoxylic acids (III; R = H and OMe respectively, besides oxalic acid, was obtained, but the acids were not isolated and characterised owing to lack of material. Condensation with *o*-phenylenediamine and subsequent alkaline fission (Schönberg and Sina, *J.*, 1946, 601) gave 2-2′-methoxybenzylbenziminazole (IV), also obtained from *o*-methoxyphenylacetic acid. This reaction establishes that the methoxyl group is attached to the benzene ring which is close to the ester group.

Experimental

Lepraria flava (*Schreb*) *Ach.* (*Pinastric Acid*).—Since complete separation of the lichen from the bark was not feasible whereas the bark contained no extractable matter except wax, the mixture of the two was extracted 4 times with cold light petroleum (b. p. 40—60°), 24 hr. each time. The combined extracts were filtered and concentrated to 50 c.c. An orange-yellow solid separated and next morning was filtered off and washed with small amounts of light petroleum to remove adhering wax. It crystallised from ether–light petroleum as golden-yellow stout rectangular prisms, m. p. 204—205°, was readily soluble in ether and hot ethyl alcohol and sparingly so in cold alcohol, dissolved in aqueous sodium hydrogen carbonate, carbonate, and hydroxide and was precipitated unchanged on acidification, and gave no colour with ferric chloride or bleaching powder, and an orange colour with concentrated sulphuric acid (Found : C, 67·9; H, 4·4. Calc. for $C_{20}H_{16}O_6$: C, 68·2; H, 4·5%). It did not depress the m. p. of pinastric acid. The acetate, prepared by boiling acetic anhydride, crystallised from ethyl acetate as pale yellow needles, m. p. 172—173° (cf. Zopf, *loc. cit.*).

Lepraria citrina *Schaer : Isolation of Leprapinic Acid.*—The lichen along with the bark was extracted with cold light petroleum as in the previous case. The solid obtained on concentration of the extract crystallised from ether–light petroleum as golden-yellow long rectangular tablets, m. p. 159—160°. It was soluble in aqueous sodium hydrogen carbonate from which it was reprecipitated by acid, and in ethyl alcohol or ether, but sparingly so in light petroleum. It gave no colour with ferric chloride or bleaching powder, and a deep yellow colour with sulphuric acid (Found : C, 68·2; H, 4·7; OMe, 18·2. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·5; 2OMe, 17·6%).

Hydrolysis to 2-methoxypulvinic acid. Leprapinic acid (0·25 g.), barium hydroxide (0·5 g.), and water (15 c.c.) were refluxed for 15 min. On cooling and acidification, a copious yellow precipitate of *2-methoxypulvinic acid* was obtained. This was dried and crystallised from dry benzene, yielding golden-yellow thick rhombohedral plates and prisms, m. p. 213—214° (Found : C, 67·6; H, 4·6. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·1%).

2-Methoxypulvinic dilactone. The above acid (100 mg.) was refluxed with acetic anhydride (2·5 c.c.) for ½ hr. and the clear yellow solution cooled in ice; the yellow crystals that separated were filtered off, washed with a small quantity of ether, and crystallised from benzene, yielding lemon-yellow elongated rectangular prisms of the *dilactone*, m. p. 172—173° (Found : C, 71·2; H, 4·1; OMe, 9·8. $C_{19}H_{12}O_5$ requires C, 71·2; H, 3·8; 1OMe, 9·7%).

Oxidation of leprapinic acid. (*a*) Leprapinic acid (150 mg.), water (15 c.c.), potassium permanganate (300 mg.) and anhydrous sodium carbonate (150 mg.) were refluxed for 2 hr. The mixture was then cooled and acidified (sulphuric acid), and sulphur dioxide passed in till the mixture was colourless. It was then extracted with ether and the extract evaporated. A colourless residue (A) was obtained which melted indefinitely between 68° and 96° and gave no colour with ferric chloride.

The mixture (A) (75 mg.), acetic anhydride (1 c.c.), and hydriodic acid (*d* 1·7, 1 c.c.) were refluxed for 1½ hr., poured into an ice-cold saturated solution of sulphur dioxide, and extracted with ether. By evaporation of the ether, a colourless solid (B) was obtained, giving a violet colour with alcoholic ferric chloride and with methyl alcohol and sulphuric acid the smell of methyl salicylate.

The acid (B) (50 mg.) was refluxed with anhydrous acetone (10 c.c.), methyl sulphate (excess), and sodium hydrogen carbonate (250 mg.) for 4 hr. (Saraiya and Shah, *Current Sci.*, 1949, 18, 218). The acetone solution was filtered, evaporated, treated with cold water, and left overnight in the refrigerator. The esters were extracted with ether, and the ether extract

was washed with aqueous 5% sodium hydroxide (2 × 25 c.c.) (aqueous solution D; ether solution C). The solution (C) was evaporated, and the residue refluxed with aqueous 5% sodium hydroxide (20 c.c.) for 1 hr., cooled, acidified (hydrochloric acid), and extracted with ether which removed a colourless material soluble in aqueous sodium hydrogen carbonate and giving no ferric chloride colour. After sublimation in vacuum, this formed colourless needles m. p. 122° alone or mixed with benzoic acid. Circular paper chromatography at 35° (Whatman No. 1) with ammonia saturated with butan-1-ol as the solvent and a buffered solution of *p*-bromophenol-blue as indicator (Fewster and Hall, *Nature*, 1951, **168**, 78) gave only one ring with R_F 0·59, which agreed with the value given by benzoic acid.

The solution (D) was acidified and extracted with ether. The ether extract on being subjected to the treatment given to (C) left a brownish residue, soluble in aqueous sodium hydrogen carbonate and giving a violet ferric reaction. On sublimation in vacuum it deposited colourless needles, m. p. 158° alone or mixed with salicylic acid. In circular paper chromatography at 30° with 0·1% alcoholic ferric chloride as the indicator it gave a ring with R_F 0·68 agreeing with salicylic acid.

(*b*) Leprapinic acid (100 mg.) was oxidised by Spiegel's method (*Ber.*, 1881, **14**, 1689) (2N-potassium permanganate, 50 c.c.; aqueous 5% sodium hydroxide, 25 c.c.) in the cold for 4 hr. The solution was acidified and sulphur dioxide passed in. Extraction with ether and evaporation of the extract gave an oil. Its solution in acetone was examined by paper chromatography at 35° with *p*-bromophenol-blue as indicator. Two rings were visible, one sharp with R_F 0·30 (oxalic acid), the other diffuse having R_F 0·57—0·62. Phenylglyoxylic acid gave a sharp ring with R_F 0·59. It seemed therefore that this was present in the degradation products along with its methoxy-analogue having a similar R_F value.

Condensation of leprapinic acid with o-phenylenediamine. Leprapinic acid (0·2 g.), *o*-phenylenediamine (0·15 g.), and *NN*-dimethylaniline (10 c.c.) were refluxed at 200—210° for 4 hr. and, after cooling, poured into dilute acid (50 c.c.). The brown solid was filtered off, washed with dilute acid, then with water, and dried. The *product* crystallised from ethyl acetate as small orange-red prisms, m. p. 271—272° (decomp.) (Found: C, 73·3; H, 5·1. $C_{25}H_{18}O_4N_2$ requires C, 73·2; H, 4·4%). It was soluble in dilute aqueous potassium hydroxide, giving a yellow solution from which it was reprecipitated by acid. It was difficultly soluble in benzene and ethyl alcohol, but very soluble in ethyl acetate.

This product was refluxed with alcoholic 10% potassium hydroxide (5 c.c.) for 5 hr. Colourless potassium salts were then filtered off. The filtrate was concentrated under reduced pressure. Colourless crystals separated. When washed with water and dried, they had m. p. 186—187° alone or mixed with 2-2′-methoxybenzylbenziminazole (below). A micro-Zeisel test was positive. The mixed m. p. with 2-benzylbenziminazole (Walther and Pulawski, *J. prakt. Chem.*, 1899, **59**, 253), m. p. 189°, was considerably depressed.

2-2′-Methoxybenzylbenziminazole.—Equal quantities of *o*-methoxyphenylacetic acid and *o*-phenylenediamine were heated at 200—210° in the presence of *NN*-dimethylaniline for 4 hr., and dimethylaniline then distilled off at 68—70°/8 mm. The brownish residue was washed with a small quantity of dilute hydrochloric acid and crystallised from dilute alcohol, yielding the *product* as colourless thick rectangular plates, m. p. 186—187° (Found: C, 75·3; H, 6·2. $C_{15}H_{14}ON_2$ requires C, 75·6; H, 5·9%), sparingly soluble in ether but highly soluble in alcohol and acetic acid.

We express our gratitude to Professor S. Shibata of Tokyo University for samples of pinastric acid and 3-methoxypulvinic dilactone, and to Mr. D. D. Awasthi and Dr. G. A. Llano for the botanical identification of the lichen samples.

UNIVERSITY OF DELHI, DELHI. [*Received, April 28th*, 1955.]

Compounds Formed between Hydrogen Peroxide and Sulphates, Selenates, and Tellurates in Aqueous Solution.

By S. PANI and (the late) HENRY TERREY.

[Reprint Order No. 6382.]

The following compounds have been prepared by crystallisation from or by precipitation (on addition of ethyl alcohol) from aqueous solutions of hydrogen peroxide and the corresponding sulphate or selenate: $Na_2SO_4,0{\cdot}5H_2O_2,H_2O$; $(NH_4)_2SO_4,H_2O_2$; $Na_2SeO_4,0{\cdot}5H_2O_2,H_2O$; $(NH_4)_2SeO_4,H_2O_2$; and K_2SeO_4,H_2O_2—of which, the selenates are new. The formation of all these compounds and also of Na_2SO_4,H_2O_2 has been confirmed by phase-diagram studies at 20°. No evidence has been found for the existence of analogous lithium, rubidium, or cæsium compounds. The compounds reported are probably perhydrates.

The following compounds have been prepared by precipitation from aqueous solutions containing tellurates and hydrogen peroxide on addition of ethyl alcohol: $LiH_4TeO_{7{\cdot}5},2H_2O$; $LiH_4TeO_7,2H_2O$; $Na_2H_4TeO_6,0{\cdot}5H_2O$; $Na_2H_4TeO_{7{\cdot}5},0{\cdot}5H_2O$; $K_2H_4TeO_{8{\cdot}5}$; and $K_2H_4TeO_8$. These may be peroxytellurates.

ATTEMPTS have been made by various workers to prepare peroxyselenic acid and the corresponding alkali salts. Brown reported the formation of potassium peroxyselenates by an electrolytic method (*J. Amer. Chem. Soc.*, 1901, **23**, 358), but Dennis and Koller (*ibid.*, 1919, **41**, 964) were unable to confirm this. Worsley and Baker (*J.*, 1923, **123**, 2874) stated that peroxyselenic acid was formed by the action of hydrogen peroxide on either selenium trioxide or chloroselenic acid which they prepared from the trioxide. Since other workers have failed to repeat the preparation of selenium trioxide reported by these authors, it seems unlikely that a preparation of peroxyselenate was in fact achieved.

The preparation of potassium peroxyselenates by electrolytic methods under conditions most favourable to the formation of peroxy-compounds (*e.g.*, high current density, low temperature, presence of fluoride, etc.) was tried, but without success. The amount of oxygen evolved at the anode indicated that the whole of the current was utilised for the decomposition of water.

Compounds containing active oxygen and selenate have been prepared, however, and these seem to be similar to the compounds $Na_2SO_4,H_2O,\frac{1}{2}H_2O_2$ and $(NH_4)_2SO_4,H_2O_2$ reported by Willstätter (*Ber.*, 1903, **36**, 1828) whose work has been confirmed in the present studies which have included some phase-diagram studies. Tellurates containing active oxygen have also been obtained and some, at least, of these appear to be true peroxytellurates.

EXPERIMENTAL

Preparation of Compounds containing Active Oxygen.—Three methods of preparation have been used:

(1) A solution of the appropriate sulphate or selenate in 30% hydrogen peroxide was allowed to crystallise over concentrated sulphuric acid in a desiccator.

(2) A solution of selenate or tellurate in 30% hydrogen peroxide was treated with alcohol to cause precipitation.

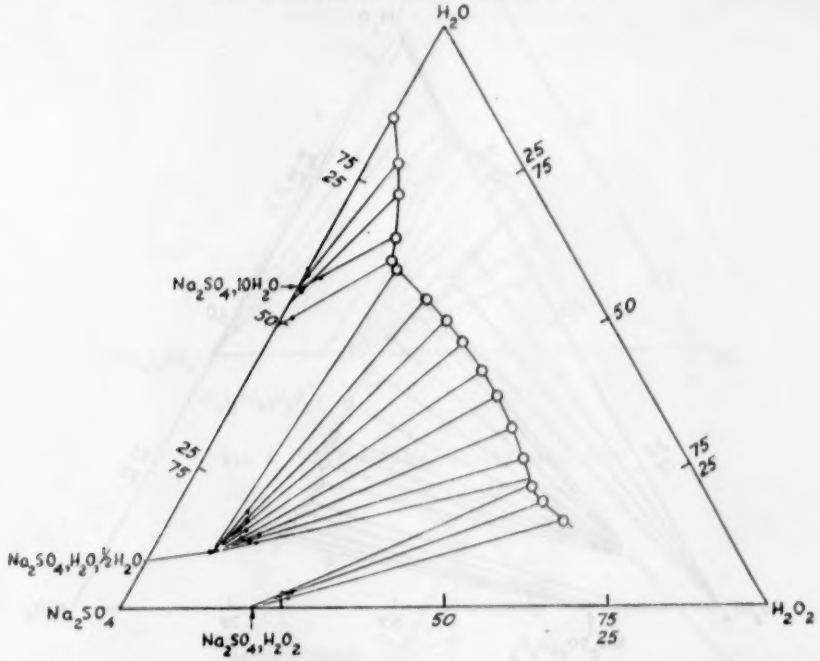
(3) A solution of alkali-metal tellurate (2 g.) in 80% hydrogen peroxide (15—20 c.c.) was treated with excess of alcohol and set aside (an oil was obtained in the case of potassium and sodium tellurates, whereas lithium tellurate yielded a fine precipitate). The supernatant clear liquid was decanted, fresh alcohol was added, and the whole set aside until (in the case of the potassium and sodium compounds) a solid material was obtained (usually after 12—18 hr.). The solid was powdered, suspended in alcohol, filtered, washed repeatedly first with alcohol, then with ether until the filtrate was free from hydrogen peroxide, and dried in a vacuum over phosphoric oxide.

Analysis.—The active oxygen was determined by titrating the acidified solution with standard potassium permanganate.

Ammonia (in the ammonium compounds) was determined by distillation with sodium hydroxide: ammonia evolved was absorbed in standard sulphuric acid (known volume) and estimated by back-titration. For the estimation of selenium the method recommended by Dennis and Koller (*loc. cit.*) was used: selenium is precipitated by adding hydrazine hydrate solution to a hydrochloric acid solution of the sample at 60°. Tellurium was likewise determined gravimetrically as the element.

Sulphates containing Active Oxygen (Perhydrates).—Willstätter's reports (*loc. cit.*) of the formation of $Na_2SO_4,H_2O_2,0{\cdot}5H_2O_2$ and $(NH_4)_2SO_4,H_2O_2$ have been confirmed. Attempts to

FIG. 1. *The system,* Na_2SO_4–H_2O_2–H_2O, *at* 20°.



prepare analogous compounds from the sulphates of lithium, potassium, rubidium, and cæsium were unsuccessful.

TABLE 1. *Selenates containing active oxygen.*

	Method of prep.	No. of samples analysed	O_a (%) †	Se (%)	Na, K, or NH_3 (%)	Wt. loss at 110° (%)
(*a*)	1	3	3·55	35·23	20·15 *	15·69
	2	2	3·55	35·08	20·02 *	15·70
	$Na_2SeO_4,0{\cdot}5H_2O_2,H_2O$ requires		3·58	35·28	20·55	15·65
(*b*)	1	3	6·22	30·91	30·13 *	13·39
	2	2	6·21	30·82	30·21 *	13·43
	K_2SeO_4,H_2O_2 requires		6·27	30·94	30·65	13·23
(*c*)	1	3	7·45	36·98	15·63	16·03
	$(NH_4)_2SeO_4,H_2O_2$ requires		7·51	37·08	15·97	15·97

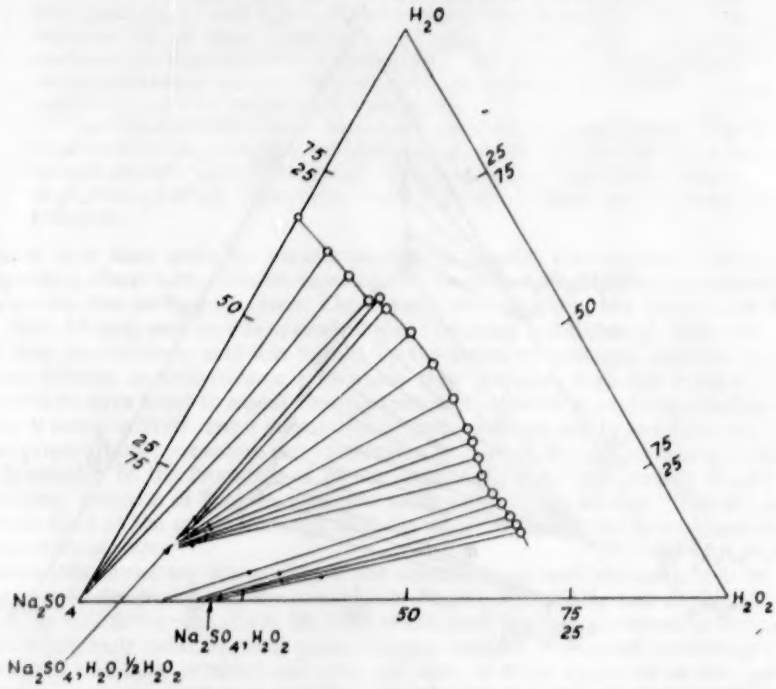
* Only one sample analysed. † O_a = active oxygen.

Selenates containing Active Oxygen.—The analytical results for the sodium, potassium, and ammonium compounds are given in Table 1. These indicate the formation of: $Na_2SeO_4,H_2O,0{\cdot}5H_2O_2$; K_2SeO_4,H_2O_2; and $(NH_4)_2SeO_4,H_2O_2$. These are colourless crystalline solids, which lose all their active oxygen at 110°, yielding a residue of the type M_2SeO_4. The aqueous solutions of these compounds oxidise ferrous to ferric salts, liberate iodine from neutral

solutions of potassium iodide (in acid solutions, selenates also liberate iodine from acidified solutions of potassium iodide), produce a blue colour with chromic acid, and decolorise acidified solutions of potassium permanganate. Hydrogen peroxide can be extracted from the solutions of these substances and, by repeated extraction with ether, all the active oxygen can be removed in this way. No corresponding compounds could be prepared from the selenates of lithium, rubidium, and cæsium by the methods described.

Tellurates containing Active Oxygen.—The analytical results for the lithium, sodium, and potassium compounds are given in Table 2. These indicate the formation of products

FIG. 2. *The system,* Na_2SO_4–H_2O_2–H_2O, *at* 35°.



of probable composition: $Li_2H_4TeO_{7\cdot5},2H_2O$; $Li_2H_4TeO_7,2H_2O$; $Na_2H_4TeO_8,0{\cdot}5H_2O$; $Na_2H_4TeO_{7\cdot5},0{\cdot}5H_2O$; $K_2H_4TeO_{8\cdot5}$; and $K_2H_4TeO_8$. Indications were obtained that potassium compounds with still higher active-oxygen contents might be formed. However, no

TABLE 2. *Tellurates containing active oxygen.*

	Method of prep.	No. of samples analysed	$M_2H_4TeO_6$ (%) *	O_a (%) †	H_2O (%)
(*a*)	3	5	78·4	7·94	13·6
	$Li_2H_4TeO_{7\cdot5},2H_2O$ requires		80·05	7·96	11·95
(*b*)	2	3	81·3	5·80	12·83
	$Li_2H_4TeO_7,2H_2O$ requires		82·24	5·45	12·27
(*c*)	3	5	86·8	10·18	3·22
	$Na_2H_4TeO_8,0{\cdot}5H_2O$ requires		86·98	10·17	2·86
(*d*)	2	5	87·37	8·12	4·51
	$Na_2H_4TeO_{7\cdot5},0{\cdot}5H_2O$ requires		89·22	7·83	2·94
(*e*)	3	10	86·90	11·57	1·53
	$K_2H_4TeO_{8\cdot5}$ requires		88·42	11·57	0
(*f*)	2	8	88·98	9·95	1·08
	$K_2H_4TeO_8$ requires		90·55	9·48	0

* Derived from % Te found. † O_a = active oxygen.

evidence was obtained of the compound $K_2TeO_5.2H_2O$ previously reported (Montignie, *Z. anorg. Chem.*, **1945**, **253**, 90).

The lithium compounds are white powders whereas the sodium and potassium compounds

FIG. 3. *The system,* $(NH_4)_2SO_4$–H_2O_2–H_2O *at* 20°.

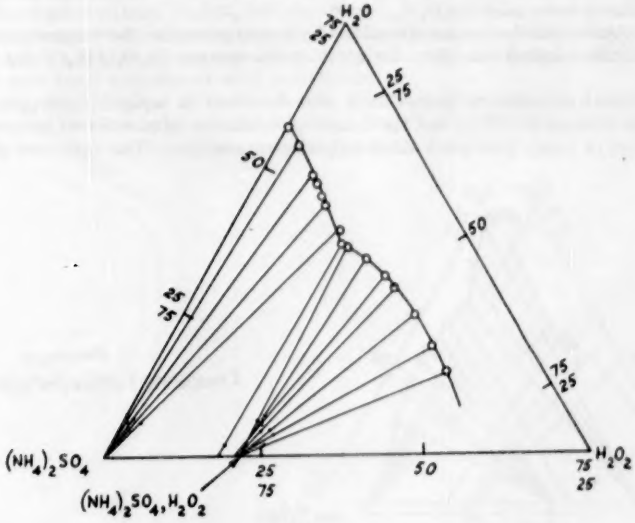
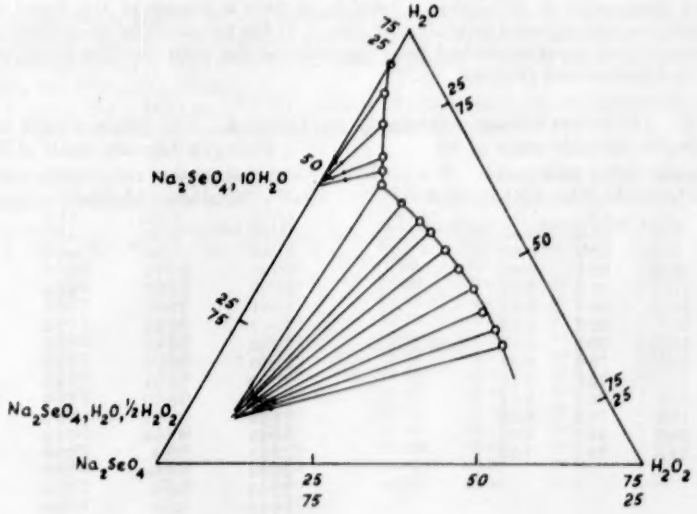


FIG. 4. *The system,* Na_2SeO_4–H_2O_2–H_2O *at* 20°



are crystalline. The active oxygen is lost on keeping or heating (below 100°). The compounds are more soluble in water than the corresponding tellurates and in general the solubility increases with the active oxygen content. The aqueous solutions of these compounds have oxidising properties similar to those of aqueous hydrogen peroxide. Ether extracts hydrogen peroxide from the solutions, but not from the dry substances (when the ether is also dry). The sodium

and potassium compounds gave at 110° a residue of composition approximating closely to $M_2H_4TeO_6$.

Systems M_2SO_4–H_2O_2–H_2O *and* M_2SeO_4–H_2O_2–H_2O.—A limited study of the system Na_2SO_4–H_2O_2–H_2O has been made by previous workers and the existence of the compound $Na_2SO_4,H_2O,0{\cdot}5H_2O_2$ reported, but the experimental data are not sufficient to enable the phase diagram to be constructed (F. Münzberg, *Lotos*, 1928, **76**, 351). Otherwise no study of these systems appears to have been made.

To avoid appreciable decomposition of the hydrogen peroxide, the temperature selected for the studies of the systems was 20°. In addition the system Na_2SO_4–H_2O_2–H_2O was studied at 35°.

Alkali sulphate or selenate (anhydrous) was dissolved in aqueous hydrogen peroxide of various concentrations (0—85%) and the saturated solution was transferred to tubes containing a small amount of finely powdered alkali sulphate or selenate. The tube was stoppered and

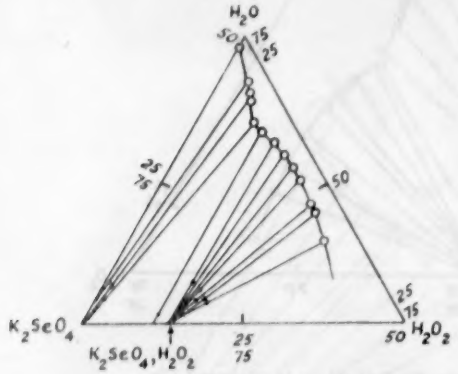


FIG. 5.
The system, K_2SeO_4–H_2O_2–H_2O *at* 20°.

placed in a thermostat at 20° ± 0·1°. After 3—4 days a sample of the liquid phase was analysed and this was repeated several hours later. If the two analyses gave identical results, it was assumed that equilibrium had been reached and the solid and the liquid phase were separated by filtration and analysed.

TABLE 3. *The system lithium sulphate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase		
Li_2SO_4 (%)	H_2O_2 (%)	Li_2SO_4 (%)	H_2O_2 (%)	Solid phase
25·20	0·00	81·6	0·00	
22·04	7·70	83·9	0·61	
20·58	12·50	82·1	0·80	
18·59	17·42	77·2	2·98	
16·74	22·58	84·3	0·98	
13·77	29·17	82·8	1·78	
9·30	44·31	80·6	4·13	Li_2SO_4,H_2O
6·98	52·86	78·4	5·99	
6·49	55·55	74·5	8·13	
4·07	68·0	81·2	3·71	
3·58	71·0	79·5	6·06	
2·30	80·8	81·5	4·73	
1·96	84·8	78·1	7·23	

TABLE 4. *The system sodium sulphate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase	
Na_2SO_4 (%)	H_2O_2 (%)	Na_2SO_4 (%)	H_2O_2 (%)
15·75	0·00	41·5	0·00
19·21	4·82	42·2	0·67
21·61	7·32	44·7	1·05
25·95	10·78	40·7	2·63
28·89	12·07	48·4	1·85
28·51	13·38	79·3	9·13
26·17	20·88	71·9	11·25
25·13	25·45	72·5	11·84
24·40	30·09	74·7	11·60
23·89	35·51	74·0	12·54
23·93	40·10	75·4	12·58
24·23	44·99	72·3	14·75
25·19	49·08	74·3	14·05
25·95	52·4	73·6	14·98
26·64	52·6	73·7	23·58
26·63	53·6	73·6	23·62
26·36	56·0	72·4	24·99
25·01	59·9	73·4	24·61
24·62	60·8	76·1	22·98

The moist solid samples were dissolved in water, and aliquot portions of the solutions so obtained and of the liquid-phase samples were used for the analyses. Hydrogen peroxide was determined by titration with standard potassium permanganate. The sulphate or selenate

was determined by carefully evaporating a portion to dryness and weighing the residue left after heating to constant weight at 110°.

System Li_2SO_4–H_2O_2–H_2O *at* 20°.—The results which are given in Table 3 indicate that the stable solid phase over the whole range of hydrogen peroxide concentration studied is $Li_2SO_4.H_2O$. Again no evidence was found for compounds containing active oxygen.

System Na_2SO_4–H_2O–H_2O *at* 20°.—The results which are given in Table 4 and Fig. 1 show the formation of three solid phases, $Na_2SO_4.10H_2O$; $Na_2SO_4.H_2O,0{\cdot}5H_2O_2$; and $Na_2SO_4.H_2O_2$, the last of which is now reported for the first time. The fact that the tie-lines indicating the region of stability of $Na_2SO_4.10H_2O$ do not meet very sharply may be attributed to the formation of solid solutions with lower hydrates or with perhydrates.

System Na_2SO_4–H_2O_2–H_2O *at* 35°.—The results which are given in Table 5 and Fig. 2 again show the formation of three solid phases, Na_2SO_4; $Na_2SO_4.H_2O,0{\cdot}5H_2O_2$; and $Na_2SO_4.H_2O_2$, and provide further confirmation of the existence of the last compound.

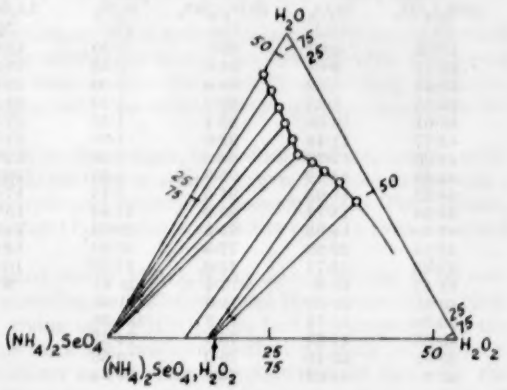


FIG. 6.
The system, $(NH_4)_2SeO_4$–H_2O_2–H_2O *at* 20°.

System K_2SO_4–H_2O_2–H_2O *at* 20°.—The results (Table 6) indicate the separation of one solid phase only, namely, K_2SO_4. No evidence was found for compounds containing active oxygen.

System $(NH_4)_2SO_4$–H_2O_2–H_2O *at* 20°.—The results (Table 7, Fig. 3) show the solid phases to be $(NH_4)_2SO_4$ and $(NH_4)_2SO_4.H_2O_2$.

System Li_2SeO_4–H_2O_2–H_2O *at* 20°.—The results (Table 8) indicate the formation of Li_2SeO_4 and $Li_2SeO_4.H_2O$, but not of compounds containing active oxygen.

TABLE 5. *The system sodium sulphate–hydrogen peroxide–water at* 35°.

Liquid phase		Moist solid phase	
Na_2SO_4 (%)	H_2O_2 (%)	Na_2SO_4 (%)	H_2O_2 (%)
33·06	0·00	91·2	0·00
31·54	7·54	93·0	0·90
30·54	12·77	85·0	2·81
29·43	18·11	88·3	2·99
27·99	19·52	74·8	10·47
27·54	21·76	76·3	10·41
26·65	23·89	72·4	11·62
26·07	27·29	77·3	10·76
25·61	33·25	76·3	11·32
25·04	39·87	73·6	13·29
25·43	44·77	73·3	14·09
25·65	46·76	70·9	16·52
25·84	47·92	74·8	13·60
26·22	48·75	75·1	14·16
27·65	50·7	77·8	12·65
26·07	47·56	75·5	13·23
27·36	54·3	71·2	23·68
26·08	56·3	67·2	28·30
26·71	58·8	78·0	21·29
26·35	60·7	67·3	29·52
26·28	61·8	60·6	35·18

TABLE 6. *The system potassium sulphate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase		
K_2SO_4 (%)	H_2O_2 (%)	K_2SO_4 (%)	H_2O_2 (%)	Solid phase
10·00	0·00	98·2	0·00	
13·78	4·12	87·5	0·63	
16·78	8·35	91·4	1·00	
19·40	12·10	86·0	0·61	
23·12	15·57	89·7	2·00	
23·89	18·45	91·0	2·33	
24·83	20·11	93·6	1·89	K_2SO_4
28·31	24·12	90·7	3·36	
31·41	28·17	95·7	1·81	
35·93	33·66	94·0	3·05	
41·09	39·29	93·0	4·75	
44·36	43·85	81·5	6·60	

System Na_2SeO_4–H_2O_2–H_2O *at* 20°.—The results (Table 9, Fig. 4) show the solid phases to be $Na_2SeO_4,10H_2O$ and $Na_2SeO_4,H_2O,0{\cdot}5H_2O_2$. No compound analogous to Na_2SO_4,H_2O_2 was found.

System K_2SeO_4–H_2O_2–H_2O *at* 20°.—In contrast to the corresponding potassium sulphate system, the existence of a compound containing active oxygen was established, namely, K_2SeO_4,H_2O_2 (Table 10, Fig. 5). The other solid phase found was K_2SeO_4.

System $(NH_4)_2SeO_4$–H_2O_2–H_2O *at* 20°.—This is similar to the corresponding ammonium sulphate system, and the solid phases found were $(NH_4)_2SeO_4$ and $(NH_4)_2SeO_4,H_2O_2$ (Table 11, Fig. 6).

TABLE 7. *The system ammonium sulphate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase	
$(NH_4)_2SO_4$ (%)	H_2O_2 (%)	$(NH_4)_2SO_4$ (%)	H_2O_2 (%)
42·93	0·00	93·0	0·00
43·17	3·04	93·6	0·35
43·44	8·02	93·0	1·00
43·54	9·23	92·2	1·33
43·61	10·00	93·4	1·30
43·77	11·44	92·0	1·60
44·00	12·73	94·5	1·30
44·35	14·79	93·3	1·69
44·22	17·03	91·5	2·70
44·94	18·74	80·9	17·44
44·50	19·85	73·3	20·24
43·85	22·29	72·5	20·87
42·88	23·71	72·0	21·09
41·43	27·90	73·4	21·61
40·81	30·20	74·0	21·94
40·28	35·63	72·3	23·30
40·02	41·37	75·4	24·27
40·32	42·18	76·0	22·55
40·40	45·62	74·6	23·54

TABLE 8. *The system lithium selenate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase		
Li_2SeO_4 (%)	H_2O_2 (%)	Li_2SeO_4 (%)	H_2O_2 (%)	Solid phase
40·64	0·00	85·0	0·00	
38·29	4·03	81·0	0·77	
35·42	9·61	85·3	0·83	
33·42	13·15	87·3	0·72	
29·86	19·88	83·0	2·55	Li_2SeO_4,H_2O
27·77	24·29	85·8	1·36	
22·59	35·56	87·1	1·77	
19·68	43·08	86·8	2·44	
17·36	46·62	80·0	5·40	
15·29	51·1	77·3	13·36	
14·96	52·9	87·1	7·75	
12·61	58·9	78·1	14·06	Li_2SeO_4
10·42	64·4	82·7	11·43	
8·26	71·5	85·7	11·05	

TABLE 9. *The system sodium selenate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase	
Na_2SeO_4 (%)	H_2O_2 (%)	Na_2SeO_4 (%)	H_2O_2 (%)
30·11	0·00	46·42	0·00
33·79	1·15	47·03	0·30
36·59	4·19	45·71	1·51
39·63	7·10	46·42	3·00
40·27	8·28	46·49	3·62
41·88	9·24	78·6	7·88
40·08	14·36	79·3	8·50
39·04	18·54	78·1	9·39
38·50	21·03	79·4	9·15
37·51	24·91	79·8	9·32
36·85	28·82	78·4	10·29
36·53	32·73	77·7	10·07
37·12	36·14	76·7	12·27
36·64	39·99	79·5	11·05
37·35	40·99	79·0	11·49
36·89	42·55	77·8	12·62
39·71	46·47	73·1	17·58

TABLE 10. *The system potassium selenate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase	
K_2SeO_4 (%)	H_2O_2 (%)	K_2SeO_4 (%)	H_2O_2 (%)
52·1	0·00	94·3	0·00
53·7	4·20	92·3	0·70
54·3	5·20	94·0	0·65
54·8	6·01	92·6	1·00
55·9	8·56	91·4	1·60
56·4	8·93	94·7	1·13
56·2	10·81	87·8	10·98
55·0	13·60	82·2	13·36
54·5	16·19	81·3	13·83
54·5	18·49	79·6	14·46
54·2	20·98	79·4	14·97
54·5	24·82	80·8	15·29
54·9	26·11	79·5	16·31
55·9	30·00	79·0	17·43

TABLE 11. *The system ammonium selenate–hydrogen peroxide–water at* 20°.

Liquid phase		Moist solid phase		Liquid phase		Moist solid phase	
$(NH_4)_2SeO_4$ (%)	H_2O_2 (%)	$(NH_4)_2SeO_4$ (%)	H_2O_2 (%)	$(NH_4)_2SeO_4$ (%)	H_2O_2 (%)	$(NH_4)_2SeO_4$ (%)	H_2O_2 (%)
54·1	0·00	93·7	0·00	54·0	15·57	85·1	12·45
54·5	2·62	90·6	0·80	52·5	18·66	79·3	16·18
54·7	5·26	92·0	0·98	52·5	19·23	80·5	16·21
54·7	7·96	91·5	1·50	51·6	21·79	79·7	16·61
54·8	10·71	92·0	1·85	50·5	25·98	79·7	18·24
55·7	12·87	93·5	1·79				

Systems containing Tellurates.—Attempts to extend these studies to systems containing tellurates were unsuccessful. The solubilities of lithium and sodium tellurates in hydrogen peroxide solutions were found to be greater than in pure water. Sodium and potassium tellurates were in fact highly soluble in aqueous hydrogen peroxide, to give pale yellow viscous solutions from which no solid material crystallised.

Discussion

Sulphates and Selenates containing Active Oxygen.—Compounds of this class have been found in the cases of the sulphates and selenates of sodium and ammonium and of potassium selenate, and are of two types: (1) $M_2SO_4,0{\cdot}5H_2O_2,H_2O$ or $M_2SeO_4,0{\cdot}5H_2O_2,H_2O$ (M = Na); (2) M_2SO_4,H_2O_2 (M = Na or NH_4) or M_2SeO_4,H_2O_2 (M = K or NH_4)—the possibility that Na_2SeO_4,H_2O_2 may be formed at higher hydrogen peroxide concentrations (Fig. 4) cannot be ruled out.

The phase diagrams for the corresponding sulphate and selenate systems are, in general, similar, apart from the differences of the solubilities of the two series of salts in aqueous hydrogen peroxide. The selenates are more soluble than the corresponding sulphates, particularly in the case of the potassium salts, for which the phase diagrams show the greatest difference.

Lithium sulphate and selenate differ from the sodium, potassium, and ammonium salts, not only in failing to form any compounds containing active oxygen, but also in showing a rapid fall in solubility with rise in hydrogen peroxide concentration. The sodium, potassium, and ammonium salts show a slight fall or rise in solubility only, or even a marked rise in solubility (K_2SO_4).

The sulphates of the second type listed above (M_2SO_4,H_2O_2) do not appear to be salts of Caro's acid (*e.g.*, M_2SO_5,H_2O) since according to Willstätter and Hauenstein (*Ber.*, 1909, **42**, 1839) this acid is monobasic only, giving salts $MHSO_5$. In fact the properties of the sulphates and selenates described in this work are consistent with their being perhydrates. If so, then the absence of similar rubidium and cæsium compounds is in line with the reluctance of these to crystallise with water (or presumably, hydrogen peroxide) of crystallisation. However, it is not possible on the basis of the evidence available to establish unambiguously the structures of these compounds.

Tellurates containing Active Oxygen.—The potassium compounds are anhydrous and the amount of water present in the sodium compounds is not sufficient to allow all the active oxygen to be present as hydrogen peroxide of crystallisation. Evidently these compounds are salts of true peroxytelluric acids. The similarity of the lithium compounds to those of potassium and sodium suggests that they are of the same class (*e.g.*, $[Li,H_2O]_2[H_4TeO_{7{\cdot}5}]$), although it is possible here to ascribe to them a perhydrate formula.

This paper was prepared by Dr. J. E. Salmon from a draft by Professor H. Terrey.

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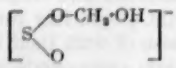
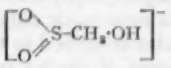
An Accurate Determination of the Structure of Sodium Hydroxymethanesulphinate (Rongalite).

By Mary R. Truter.

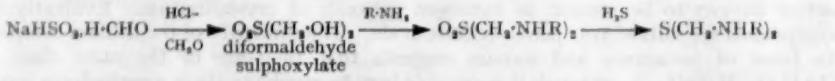
[Reprint Order No. 6161.]

A crystal-structure determination has shown that the compound of empirical formula $NaHSO_2,H{\cdot}CHO,2H_2O$ is sodium hydroxymethanesulphinate dihydrate. The bond lengths in the anion, $HO{\cdot}CH_2{\cdot}SO_2$ are C–O = 1·409 Å, S–C = 1·838 Å, S–O = 1·495 Å and 1·511 Å, all with standard deviations of 0·01 Å or less; the bonds to the sulphur atom are arranged pyramidally, the angles being O–S–O 108°36′ and C–S–O 101°25′ and 100°7′, while the O–C–S angle is 110°0′.

When a mixture of sodium hydrogen sulphite and formaldehyde is reduced by zinc dust in alkaline aqueous solution, a strongly reducing compound can be salted out. This compound is generally known as " Rongalite C " or " Formosul," the names under which it is sold as a reducing agent for vat dyeing. Although the empirical formula $NaHSO_2,H{\cdot}CHO$, sodium formaldehyde sulphoxylate, is well established, the nature of the link between the inorganic and the organic portions of the compound has not hitherto been known. Two views are possible, each consistent with part of the chemical evidence but neither regarded, so far, as entirely acceptable. The parent compound, the hypothetical sulphoxylic acid, may be formulated either (*a*) as $S(OH)_2$ containing bivalent sulphur and analogous to SCl_2 or (*b*) as $H{\cdot}SO{\cdot}OH$, a compound of quadrivalent sulphur analogous to the organic sulphinic acids. Accordingly, the formaldehyde sulphoxylate ion may be (I) or (II).

(I)   (II)

The objection to the formulation (I) is that sodium formaldehyde sulphoxylate does not react in the diagnostic manner with thiosulphate to form higher thionates. Moreover, the wavelengths of the K_α *X*-ray fluorescence spectrum are close to those of known quadrivalent sulphur compounds (Faessler and Goehring, *Naturwiss.*, 1943, **31**, 567). The main objection to formulation (II) is evident from the reactions:



If formula (II) is correct, $O_2S(CH_2{\cdot}NHR)_2$ appears to be a sulphone, a type of compound which cannot usually be reduced by hydrogen sulphide. [This objection is not insuperable, however, since the amine might activate the methylene group; it would then be possible for the C–S bond to break yielding a $\cdot(CH_2{\cdot}NHR)$ radical which would react with some of the sulphur present in the hydrogen sulphide solution.] Treatment of sodium formaldehyde sulphoxylate with sodium hydrogen sulphite gives a mixture of sodium hydrosulphite (dithionite), $Na_2S_2O_4$, and formaldehyde–sodium hydrogen sulphite, $NaHSO_3,CH_2O$. Several lines of argument show that the latter almost certainly has the constitution $Na^+(O_3S{\cdot}CH_2{\cdot}OH)^-$; *e.g.*, acetylation of the potassium salt gives the salt $CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}SO_3K$ identical with the product obtained from potassium iodomethanesulphonate, $I{\cdot}CH_2{\cdot}SO_3K$ (Lauer and Langkammerer, *J. Amer. Chem. Soc.*, 1935, **57**, 2360). The dimeric formula $Na_2S_2O_4$ of the other product is supported by cryoscopic and magnetic measurements (Klemm, *Z. anorg. Chem.*, 1937, **231**, 136); the ion may be $O{\cdot}S{\cdot}O{\cdot}SO_2$ or the symmetrical $O_2S{\cdot}SO_2$. Had formaldehyde–sodium hydrogen sulphite been the sole product of the reaction it could have been argued that formulation (II) was the more likely for the formaldehyde sulphoxylate ion, but the existence of a second reaction product of unknown structure throws doubt on the validity of this argument.

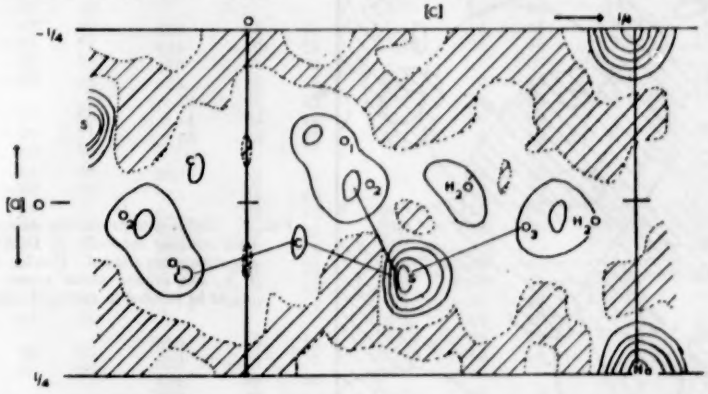
In order to explain all the chemical evidence it is necessary to postulate either

equilibrium between the two forms (I) and (II) in solution or a tendency for decomposition into formaldehyde and an unstable HSO_2^- ion. Evidence in favour of the second postulate is that the parent sulphoxylate ion itself is unstable in solution, the only known compounds, $ZnSO_2$ and $CoSO_2$, being insoluble, and that the full reducing power is only attained on warming the formaldehyde sulphoxylate solution.

The structure analysis described below shows that $NaHSO_2,H{\cdot}CHO,2H_2O$ is, in the solid state, the dihydrate of sodium hydroxymethanesulphinate with the structure (II), and it also yields accurate values of bond lengths in a type of sulphur compound not previously studied.

Determination of Atomic Positions.—The orthorhombic unit cell has the constants $a_0 = 6{\cdot}78$, $b_0 = 10{\cdot}38_5$, $c_0 = 15{\cdot}97$ Å; there are eight formula units in the general positions

FIG. 1. *Fourier projection along* [010]. *Contour intervals are* 2e/Å³ *and negative areas shaded.*



of the space group *Pbca*-D_{2h}^{15}. Absolute values of F^2 were obtained statistically from a set of relative three-dimensional intensities determined photographically.

Patterson projections along [100] and [010] proved intractable. Three-dimensional Patterson sections at $x = 0$, $x = \frac{1}{2}$, and $y = \frac{1}{2}$ showed symmetry-related peaks which could be identified as S–S and Na–Na vectors; the fractional co-ordinates obtained were S at 0·108, 0·273, 0·102, and Na at 0·00, 0·10, 0·25 or 0·25, 0·10, 0·25. The (0*kl*) projection was considered first. Calculation of structure factors with sodium and sulphur only showed that at least some of the positions of the other six atoms (5 oxygen and 1 carbon) would have to be determined before Fourier synthesis was possible. By trial and error, and with the help of some weaker Patterson peaks, two atoms were located and designated $O_{(1)}$ and $O_{(2)}$, both being sufficiently near the sulphur to be part of the anion. The first value of $R = \Sigma|F_0 - F_c|/\Sigma|F_0|$ was 0·46; successive Fourier refinements reduced this to 0·22. The atomic arrangement viewed along [100] is shown in Fig. 3 and in Fig. 2 as a sketch on the (0*kl*) difference projection; clearly formula (II) is correct and the compound is sodium hydroxymethanesulphinate.

For the (*h*0*l*) projection the Patterson–Harker section gave unambiguously the sulphur parameters only, so that the others had to be determined by trial and error. The correct model gave $R = 0{\cdot}22$ and the electron-density projection shown in Fig. 1. It can be seen that the Na^+ ion is not exactly at $z = \frac{1}{4}$ and again there is an overlap of two glide-related ions giving an apparent value of $x_{Na} = \frac{1}{4}$. This projection shows the pyramidal shape of the anion.

This arrangement gave $R = 0{\cdot}24$ for (*hk*0) planes and the projection along [001] was computed; as expected, none of the oxygen atoms was resolved but the Na^+ ion appeared at $x = 0{\cdot}276$, the previous approximate value of $\frac{1}{4}$ being due to the superposition of the two peaks at 0·27 and 0·23.

Refinement by Three-dimensional Methods.—All three-dimensional calculations were

carried out on the Manchester University digital computer with programmes devised by Ahmed and Cruickshank (*Acta Cryst.*, 1953, **6**, 765) and modified for *Pbca* by Dr. P. J. Wheatley.

Structure factors were calculated for all (*hkl*) planes, the initial value of R being 0·296. Co-ordinate shifts were determined by the method of differential synthesis, termination-of-series errors being corrected by the back-shift method. Successive refinements were carried out until the shifts were less than 0·01 Å, the agreement index for the observed planes then being $R = 0{\cdot}152$. The final calculated structure factors, with those observed for comparison, are shown in Table 1; the indices of reflections not observed have been omitted, and the indices are arranged in groups first with $h + k$ and $k + l$ even, then $h + k$ even and $k + l$ odd, then $h + k$ odd and $k + l$ even, last $h + k$ and $k + l$ odd.

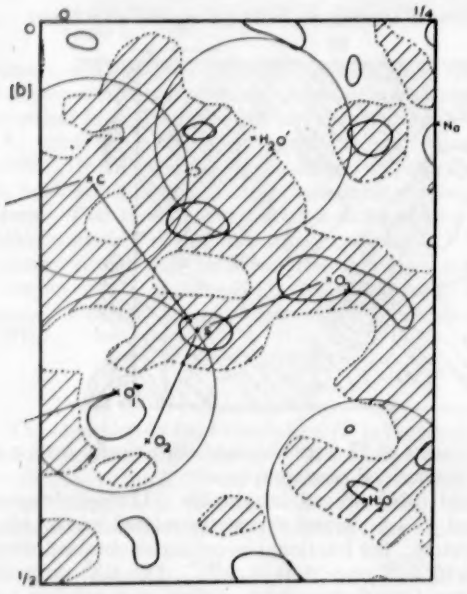


FIG. 2. *Difference projection along* [100] *with contour intervals of* 1e/Å^3 *and negative areas shaded. Circles, radius* 1 Å, *are drawn about atoms which might be bonded to hydrogen atoms.*

In Table 2 are given the final co-ordinates and their standard deviations calculated from Cruickshank's equation (*Acta Cryst.*, 1949, **2**, 65)

$$\sigma(x) = \frac{1}{V} \cdot \frac{2\pi}{a} [h^2(\Delta F)^2]^{\frac{1}{2}} / (\partial^2\rho/\partial x^2)$$

$\sigma(x)$ is the standard deviation in x, V is the volume of the unit cell, $\partial^2\rho/\partial x^2$ is the curvature of the atom in the x direction, and ΔF was taken as $|F_0 - F_c|$. In Table 2 are also shown the peak electron densities at the centres of the atoms, the ratio between these values and those obtained from an identical computation using the calculated instead of the observed structure factors (ρ_0/ρ_c), and similarly the ratio observed/calculated for the mean curvatures $\partial^2\rho/\partial x_i^2$ where $x_i = x,y,z$.

The scattering factors used were those for Na^+ and neutral sulphur ("International Tables for the Determination of Crystal Structures," Borntraeger, Berlin, 1935) and those calculated by McWeeny (*Acta Cryst.*, 1951, **4**, 513) for oxygen and carbon. The original Wilson plot for (0*kl*) had indicated that no temperature factor was required; however, the relation between the observed and the calculated values of the curvatures ($\partial^2\rho/\partial x_i^2$) of the atoms found in three-dimensional refinement showed that some modification should be made. Finally the scattering factors were multiplied by $\exp(-B \sin^2\theta/\lambda^2)$ with $B = 0{\cdot}8 \times 10^{-16}$ cm.^{2} for Na^+ and sulphur, $1{\cdot}2 \times 10^{-16}$ cm.^{2} for carbon, and $1{\cdot}6 \times 10^{-16}$ cm.^{2} for

TABLE 1.

hkl	$F_{calc.}$	$F_{obs.}$
000	(632)	
002	−17	9
004	− 4	9
006	−116	103
008	−10	20
0,0,10	−10	23
0,0,14	−61	68
0,0,18	−10	19
0,0,20	47	50
200	204	128
202	63	57
204	−84	82
206	58	64
208	−99	84
2,0,10	42	46
2,0,12	−61	67
2,0,14	29	30
2,0,16	−18	18
400	70	63
402	−93	71
404	68	70
406	24	30
4,0,10	−62	66
4,0,14	31	34
4,0,16	44	67
4,0,18	−39	53
600	−26	40
606	49	53
6,0,14	41	62
800	39	35
806	−20	25
111	−13	10
113	20	17
115	99	72
117	−46	47
119	11	8
1,1,11	− 8	10
1,1,13	−25	24
1,1,15	−13	14
1,1,17	− 8	8
1,1,19	7	10
311	−21	19
315	45	45
317	−22	22
319	19	22
3,1,11	17	17
3,1,13	−23	21
3,1,15	−10	7
511	−14	13
513	−11	13
515	19	17
517	−18	17
519	27	30
5,1,11	11	13
5,1,15	−18	13
711	−11	10
713	—	—
7,1,11	12	17
020	−116	72
022	−90	86
024	94	83
026	15	14
028	39	43
0,2,10	−66	64
0,2,12	− 8	5
0,2,14	61	59
0,2,16	26	21
0,2,18	−24	21
0,2,20	−24	23
220	−61	50
224	− 9	14
226	13	14
228	6	8
2,2,12	−28	29
2,2,14	43	43
2,2,16	−12	15
420	81	73
424	−25	28
426	−66	72
428	37	38
4,2,10	27	32
4,2,14	−24	16
4,2,16	−24	13
620	32	31
622	21	20
624	−29	42
626	−21	21
628	6	5
6,2,10	24	26
6,2,12	− 9	11
6,2,14	− 7	8
820	−15	10
822	− 9	7
824	19	20
826	12	14
131	—	—
133	−52	48
135	−60	50
137	−12	14
139	41	44
1,3,11	24	25
1,3,13	23	28
1,3,15	9	12
1,3,17	− 4	8
1,3,19	11	14
331	8	7
337	−14	15
339	−10	11
3,3,11	−18	10
040	−71	66
042	−23	22
044	−83	90
046	29	27
048	−15	13
0,4,10	124	129
0,4,12	10	10
0,4,14	−39	41
0,4,16	−34	29
0,4,18	29	21
240	−12	13
242	−92	79
244	38	38
246	−13	16
248	24	22
2,4,10	23	33
2,4,12	36	36
2,4,14	−43	39
2,4,16	11	12
440	−91	74
444	27	29
446	65	73
151	27	23
153	−12	14
155	13	19
157	20	20
159	−60	55
1,5,11	−30	32
1,5,13	12	14
1,5,15	40	39
1,5,17	11	14
1,5,19	−24	21
351	43	40
353	−34	33
355	−30	26
357	6	12
551	35	32
060	−119	95
062	114	98
064	14	17
066	42	42
068	−58	69
0,6,10	−32	39
0,6,12	34	39
0,6,14	26	23
0,6,18	14	18
262	6	8
264	65	54
266	−51	41
268	29	27
2,6,10	−51	38
2,6,12	25	22
2,6,14	−26	26
2,6,16	12	10
460	−42	29
462	50	47
464	−45	45
666	−28	34
171	30	22
173	27	25
175	−62	49
177	27	27
179	25	26
1,7,13	−20	18
1,7,15	−45	45
1,7,17	−11	14
371	−28	24
373	28	26
375	6	18
377	32	29
379	−11	10
3,7,11	−26	22
571	−43	38
080	35	37
082	29	29
084	−36	43
086	−11	13
0,8,12	15	17
0,8,14	−14	14
280	26	23
282	21	21
284	−16	16
2,8,10	−13	14
2,8,12	11	12
191	−64	56
193	9	8
195	47	37
197	19	20
199	−27	26
1,9,11	4	12
1,9,15	12	13
395	−14	13
3,9,11	28	26
591	32	30
0,10,2	−34	33
0,10,6	−19	17
0,10,8	41	56
0,10,10	−24	32
0,10,12	23	33
2,10,0	−33	26
2,10,2	20	18
2,10,4	−41	33
2,10,6	23	18
1,11,1	22	19
1,11,3	5	8
1,11,5	−47	41
1,11,7	−22	20
1,11,9	22	22
1,11,11	19	20
3,11,1	−23	21
3,11,3	17	15
3,11,7	− 2	10
3,11,9	−14	8
5,11,1	−34	36
0,12,2	−24	20
0,12,4	26	21
0,12,8	11	19
0,12,10	−23	37
2,12,0	−21	18
2,12,4	−12	8
2,12,6	21	18
1,13,5	33	36
3,13,1	21	22
3,13,3	−12	18
0,14,0	18	31
112	−94	57
114	−37	39
116	1	8
118	54	52
1,1,10	40	41
1,1,12	−70	72
1,1,14	−28	26
1,1,16	28	27

TABLE 1. (*Continued.*)

hkl	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$
312	9	13	3,3,12	−18	28	172	36	33	0,14,1	−13	17
316	−61	69	3,3,14	−15	21	174	31	29			
318	−37	43				176	40	34	102	−44	40
3,1,10	36	43	534	−58	60	178	−26	30	106	53	52
3,1,14	16	17	536	24	34	1,7,10	−20	20	108	36	44
3,1,16	− 4	11				1,7,12	20	23	1,0,12	−66	66
			041	−43	35	1,7,16	−22	25	1,0,18	34	34
512	37	44	043	−74	78						
514	11	15	045	−46	56	372	−13	13	302	−54	45
516	−67	71	047	86	103	374	− 5	5	304	35	34
518	−51	54	049	−54	53	376	29	28	306	25	28
5,1,10	17	18	0,4,11	34	38	3,7,10	−22	18	308	76	74
5,1,12	40	42	0,4,13	−37	30				3,0,10	−26	30
5,1,14	22	23	0,4,15	29	29	081	40	39	3,0,12	−62	73
			0,4,17	11	13	083	−75	88	3,0,14	−43	48
714	− 7	4	0,4,19	20	21	085	23	22	3,0,16	31	35
716	− 8	8				087	27	40	3,0,18	21	26
718	− 4	4	241	66	63	089	52	53			
7,1,10	13	14	243	−94	84	0,8,11	−61	77	502	12	23
			245	40	43	0,8,13	−26	34	504	34	38
021	−34	41	247	− 5	16	0,8,15	−25	32	506	−27	33
023	110	81	2,4,13	16	17				508	−18	26
025	48	49	2,4,15	−10	12	281	−18	15	5,0,12	−23	34
027	45	39	2,4,17	14	16	283	30	24			
029	−118	116				285	−52	41	702	32	39
0,2,11	28	22	441	15	13	287	43	38	704	35	38
0,2,13	−39	31	443	44	47	289	−21	18	706	−56	62
0,2,15	17	9				2,8,13	−32	33	708	−40	41
0,2,17	−36	36	641	33	10				7,0,12	20	34
0,2,19	23	24				481	60	59			
			841	−11	10				215	20	21
221	67	67				681	7	12	217	−21	23
223	−54	59	152	−34	30				219	12	12
225	122	93	154	− 3	7	192	−30	30	2,1,13	15	16
227	−47	52	156	43	42	194	−10	12	2,1,15	−15	15
229	−21	20	158	9	16	196	−17	18			
2,2,11	−42	43	1,5,10	14	20				411	−47	40
2,2,13	13	14	1,5,12	−38	37	392	−20	16	413	24	22
2,2,15	−18	20	1,5,14	− 7	11	396	−19	17	415	−26	26
			1,5,16	32	30				417	9	12
421	−53	42	1,5,18	9	8	0,10,1	18	14	419	−14	17
445	−11	8				0,10,3	43	58	4,1,11	10	11
447	33	38	352	34	28	0,10,5	9	9	4,1,17	−14	17
449	−55	66	354	38	35	0,10,7	−78	96			
4,4,11	9	10	356	18	18	0,10,9	−14	12	613	−35	31
4,4,13	−29	28	358	−25	21	0,10,11	—	—	615	7	8
4,4,15	24	14	3,5,10	−15	14	0,10,13	40	63	617	−24	23
			554	41	43				619	18	17
623	−38	36				2,10,1	−25	20	6,1,11	−20	19
625	24	22	061	57	56	2,10,3	36	29	6,1,13	17	20
627	−11	10	063	19	17	2,10,7	−16	15			
629	− 1	4	067	−66	78	4,10,1	−23	23	811	−33	35
6,2,11	−14	14	069	26	25				815	−24	26
6,2,13	7	7	0,6,11	44	64	6,10,1	−22	22	817	8	10
			0,6,13	32	28						
821	11	8	0,6,15	1	7	1,11,2	− 8	8	122	54	41
823	4	7	0,6,17	−34	40	1,11,4	− 8	7	124	10	8
						1,11,6	−19	19	126	−35	39
132	128	89	263	13	16	1,11,8	15	19	128	−45	48
134	−93	73	265	−26	23				1,2,12	32	32
136	−34	40	267	− 3	13	0,12,1	−43	46	1,2,14	24	26
138	−48	50	269	15	17	0,12,3	−19	20	1,2,16	−22	20
1,3,10	18	19	2,6,11	38	33	0,12,7	62	101	1,2,18	−12	15
1,3,12	50	46	2,6,13	− 9	14	0,12,9	6	5			
1,3,18	−28	27	2,6,15	15	18				322	59	54
			2,6,17	−21	18	2,12,3	18	17	324	15	16
332	23	21				2,12,5	19	17	326	−53	57
334	−97	88	461	− 9	8	2,12,7	10	13	328	−41	45
336	21	23	463	−54	47				3,2,10	− 9	10
338	13	16				1,13,2	26	26	3,2,12	58	55
3,3,10	17	15	661	−15	25	1,13,4	26	26	3,2,14	19	22

TABLE 1. (*Continued.*)

hkl	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$	*hkl*	$F_{calc.}$	$F_{obs.}$
524	−15	15	473	−46	31	321	−41	33	650	28	29
526	7	8				323	−46	41	656	−19	32
528	16	16	671	14	13	325	−22	23			
						327	28	31	161	32	29
722	−30	29	182	−13	12	329	36	38	165	−35	31
724	−21	20	184	−11	12	3,2,11	35	36	167	− 9	12
726	26	32	1,8,12	−10	10	3,2,13	− 6	13	169	18	19
728	44	53	1,8,16	10	13				1,6,11	20	21
7,2,10	− 9	12				521	−26	20	1,6,13	−13	15
			384	−16	13	523	−27	28	1,6,15	−16	17
231	−27	22				525	12	10	1,6,17	− 9	12
233	−40	40	291	26	24	527	7	10			
235	−23	27	293	25	22	529	23	31	361	48	47
237	19	20	297	−58	44	5,2,11	− 8	10	365	−40	33
2,3,11	−12	16	299	−20	17	5,2,13	12	13	367	−25	26
2,3,15	12	16	2,9,11	28	25				369	32	30
2,3,17	24	26	2,9,13	39	33	721	−17	12	3,6,11	15	15
						725	13	12			
831	18	18	691	−12	13	727	9	10	561	7	7
						729	− 4	5			
			1,10,10	9	10	7,2,11	−11	14	761	−13	17
142	−59	53									
144	−22	25	2,11,1	−11	11	230	114	84	274	−39	36
146	7	10	2,11,3	−37	29	232	−13	14	278	13	17
148	38	37	2,11,5	19	16	234	−33	35	2,7,10	41	36
1,4,12	−12	14	2,11,7	41	30	236	−65	68	2,7,16	−17	16
1,4,14	−16	17	2,11,9	24	20	238	14	14			
1,4,16	24	21	2,11,11	−26	22	2,3,10	49	52	670	−20	20
1,4,18	6	10				2,3,12	20	23	676	32	44
			4,11,1	−12	8	2,3,14	−40	42			
342	−73	65				2,3,16	−16	18	181	−40	33
344	−36	36	1,12,2	9	8	2,3,18	11	13	183	7	11
346	25	29							185	26	28
348	33	32	3,12,2	9	8	430	25	25	187	19	18
3,4,10	21	33				434	−38	47	189	−28	23
3,4,12	−32	40	2,13,1	17	17				1,8,15	32	31
			2,13,3	31	30	634	53	41			
744	25	21							381	−53	49
			210	−134	99				385	49	39
			212	−66	62	830	−31	36	389	−17	20
251	24	25	214	64	72	836	32	48	3,8,11	−17	10
253	80	78	216	35	40				3,8,13	26	29
257	−19	22	2,1,10	−46	49	143	10	12			
259	−24	23	2,1,12	9	13	145	42	38	781	24	28
2,5,11	28	26	2,1,14	52	48	147	−15	16			
2,5,17	−32	31	2,1,16	33	26	149	−19	24	290	−21	17
			2,1,18	−19	16	1,4,11	−36	36			
451	43	41				1,4,13	10	12	690	−15	31
			410	−79	76	1,4,15	6	10			
651	−29	29	414	3	5	1,4,17	12	12	1,10,1	26	20
			416	14	15	1,4,19	−15	14	1,10,5	−33	26
162	32	30	418	−12	15				1,10,9	15	15
164	28	26	4,1,14	41	44	341	10	8	1,10,11	16	18
168	− 7	12				343	17	18	1,10,13	−14	16
1,6,10	−12	14	610	46	39	345	44	43			
1,6,12	26	23	614	−16	27	349	−45	40	3,10,1	31	26
1,6,14	−10	12	616	−59	66	3,4,11	−27	29	3,10,5	−42	34
1,6,16	− 4	10	618	20	20	3,4,13	−11	17	3,10,11	24	22
1,6,18	−23	19	6,1,10	20	20						
			6,1,12	16	19	541	22	21	5,10,1	−18	15
362	50	41	6,1,14	−15	16						
364	17	18				741	21	24	2,11,0	4	10
366	13	13	810	18	25				2,11,2	9	12
368	−35	30	812	26	30	250	−19	26			
			814	−30	33	254	60	53	1,12,1	−16	14
764	−32	38	816	−27	36	256	28	29	1,12,5	25	21
						258	−18	19	1,12,9	−15	19
271	−28	25	121	−22	20	2,5,10	−53	43			
273	−48	41	123	−42	36	2,5,12	25	26	3,12,1	−19	18
277	54	49	129	46	51	2,5,14	19	23	3,12,3	12	12
2,7,11	−19	18	1,2,13	16	18	2,5,16	13	13	3,12,5	30	23
2,7,13	−40	35	1,2,15	−19	20				3,12,7	14	12
2,7,17	24	21	1,2,19	− 6	7	454	27	24	2,13,0	11	15

oxygen. The scaling factor obtained from $\Sigma|F_c|/\Sigma|F_o|$ was 0·956 showing that the approximation to absolute values of F^2 had been good. Although the mean value of the

FIG. 3. *Projection along* [100] *with the positive direction of the* a*-axis away from the reader. Fractional* x *co-ordinates to two decimal places are marked for one asymmetric unit. Atoms at* $x \sim 0$ *are shown by thin and those at* $x \sim \frac{1}{2}$ *by thick circles.*

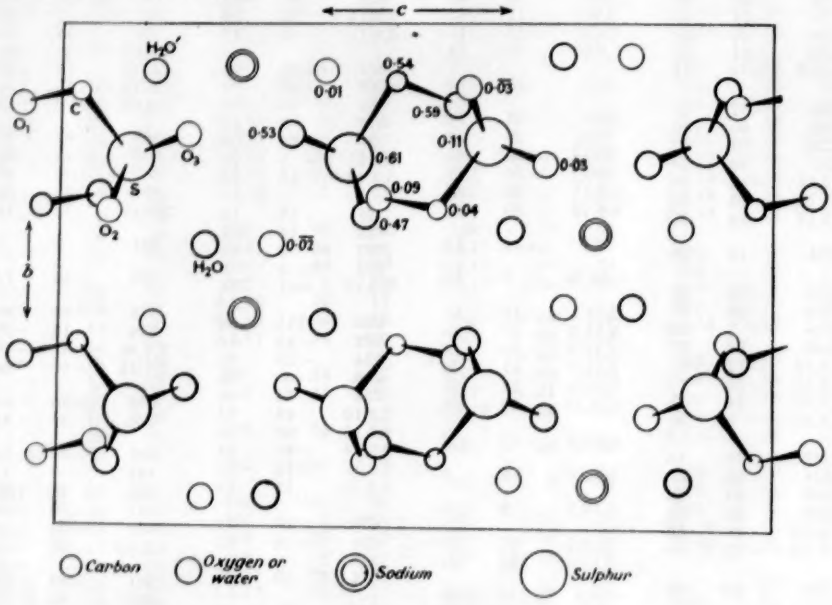


TABLE 2.

Atom	x/a	y/b	z/c	X (Å)	$\sigma(x)$ (10^4 Å)	Y (Å)
S	0·1066	0·2743	0·1012	0·722	8	2·972
Na	0·2740	0·0926	0·2557	1·858	14	1·003
C	0·0414	0·1422	0·0343	0·248	44	1·541
O_1	0·0931	0·1686	−0·0492	0·558	29	1·827
O_2	−0·0272	0·3725	0·0679	−0·163	31	4·035
O_3	0·0262	0·2299	0·1842	0·157	23	2·491
H_2O	0·4768	0·4347	0·2084	2·861	33	4·710
H_2O'	−0·0124	−0·3976	0·1379	−0·074	38	4·308

Atom	$\sigma(y)$ (10^4Å)	Z (Å)	$\sigma(z)$ (10^4Å)	ρ_o/ρ_o	e/Å³	$\partial^2\rho/\partial x_i^2$ Obs./calc.
S	29	1·617	13	0·99	41·7	1·01
Na	58	4·083	22	0·97	25·1	1·00
C	125	0·548	65	1·00	9·9	1·02
O_1	107	−0·786	40	0·99	14·1	1·03
O_2	109	1·084	44	0·93	13·5	0·96
O_3	87	2·941	53	0·96	14·7	1·06
H_2O	102	3·329	48	0·93	13·3	0·97
H_2O'	105	2·203	48	0·99	13·5	1·04

curvature is given, there is actually a slight tendency to anisotropic thermal vibration, the motion being larger in the *b*-axis direction; the mean values for all atoms are:

observed/calculated $\partial^2\rho/\partial x^2 = 1{\cdot}01 : 1$; $\partial^2\rho/\partial y^2 = 0{\cdot}98 : 1$; $\partial^2\rho/\partial z^2 = 1{\cdot}04 : 1$; $\rho = 0{\cdot}968 : 1$.

Attempted Location of Hydrogen Atoms.—Although this structure is not a promising one for the location of hydrogen atoms, the $(0kl)$ difference projection was computed, with the result shown in Fig. 2. There are peaks large enough to be hydrogen atoms but while some

are within reasonable distance of oxygen atoms others are so far away that they are obviously spurious.

It is interesting that, although the same parameters were used for calculating this projection and for a three-dimensional difference synthesis, some of the shifts indicated here are the same as those found three-dimensionally, while others differ in both magnitude and direction. This indicates that the limits of true refinement by two-dimensional methods had been reached.

Discussion of the Structure.—The structure as a whole can be visualised in terms of anions and water molecules lying at approximately $x = 0$ and $x = \frac{1}{2}$ with the Na^+ ions at $x = \frac{1}{4}$ and $x = \frac{3}{4}$ (see Fig. 1), so that projected along [100] it appears as in Fig. 3. Thin and thick circles represent atoms at approximately $x = 0$ and $x = \frac{1}{2}$ respectively; the x co-ordinates of some of the atoms are marked. Strong hydrogen bonds (2·63 Å) between $O_{(1)}$ and $O_{(2)}$ connect the anions in a spiral parallel to the a-axis, in which direction the $O_{(3)}$–Na^+ electrostatic attraction also forms a continuous link. Each $O_{(3)}$ has two Na^+ neighbours at 2·52 and 2·46 Å (the longer distance being from O at $x \sim 0$ to Na at $x \sim \frac{1}{4}$), and each Na^+ has two $O_{(3)}$ neighbours. In the c-direction the structure is held by the same Na^+–$O_{(3)}$ bonds, but in the b-direction there are only weak bonds between the ions in the two halves of the unit cell divided by the line $y = \frac{1}{2}$. These bonds are a weak hydrogen bond (2·87 Å) from $O_{(1)}$ to a water molecule with similar x-co-ordinates, and the attraction between this water molecule and the Na^+ ion. The weaker bonding along b is consistent with the somewhat greater thermal vibration indicated by the values of $\partial^2\rho/\partial y^2$.

In spite of the fact that there are so many water molecules and oxygen atoms present, the only hydrogen bonds in the structure are the two to the CH_2·OH oxygen. The bonds to $O_{(1)}$ are C–$O_{(1)}$ = 1·409 Å, $O_{(1)}$–$O_{(2)}$ = 2·63 Å, and $O_{(1)}$–H_2O = 2·87 Å, with the angles C–$O_{(1)}$–O_2 108° 42′, C–$O_{(1)}$–H_2O 134°, H_2O–$O_{(1)}$–$O_{(2)}$ 96°, indicating a pyramidal arrangement. The sodium ion is surrounded by four water molecules and two $O_{(3)}$ atoms of the anion in a distorted octahedron. The interatomic distances are shown in Table 3; the letter L refers to atoms with $z = 0$ to $\frac{1}{4}$ and M to those with $z = \frac{1}{4}$ to $\frac{1}{2}$.

TABLE 3. *Bond lengths* (Å) *and angles* (*standard deviations in parentheses*).

The salt.

Na–H_2O'	L 2·48	Na–$O_{(3)}$	M 2·46	$O_{(3)}$ L–$O_{(3)}$	M 3·99	$O_{(3)}$ L–H_2O	L 3·22
Na–H_2O'	M 2·46	Na–H_2O	L 2·53	$O_{(3)}$ L–H_2O'	L 3·63	$O_{(3)}$ L–H_2O'	M 3·30
Na–$O_{(3)}$	L 2·52	Na–H_2O	M 2·47	H_2O' L–H_2O	L 3·82	H_2O L–H_2O'	M 3·05

Hydroxymethanesulphinate ion.

S–C	1·838 (0·0107)	S–$O_{(3)}$	1·511 (0·0057)	$O_{(3)}$–S–$O_{(3)}$	108·5°	$O_{(3)}$–S–C	100·0°
S–$O_{(3)}$	1·495 (0·0084)	C–$O_{(1)}$	1·409 (0·0081)	$O_{(3)}$–S–C	101·5°	$O_{(1)}$–C–S	110·0°

The C–O bond length is shorter than 1·437 Å, the mean value of a number of X-ray and electron-diffraction determinations (Cox and Jeffrey, *Proc. Roy. Soc.*, 1951, *A*, **207**, 110) and therefore suggests that there may be about 12% of double-bond character in the bond. However, very few accurate measurements of C–O single bond distances have been made and it is by no means certain what precision can be assigned to the "standard" value of 1·437 Å, so that the present value may not be significantly different from it. On the other hand, the C–S bond is longer than 1·81 Å, the mean value of many determinations, and the difference is just significant with $\Delta/\sigma = 2{\cdot}6$ if there is no error in the value 1·81 Å. The curve of bond order against bond length curve for C–S given by Cox and Jeffrey (*loc. cit.*) yields on extrapolation an order 0·84 for the observed value 1·838 Å, so that the sum of the orders of the two carbon bonds is about 1·96. Although the order determined in this way is only approximate, it suggests that there may be some tendency toward dissociation into separate CH_2O molecules only loosely associated with the SO_2^- ion, thus confirming the postulate made on p. 3065.

The case of the S–O bonds is interesting. First, they are equal in spite of having very different environments; only $O_{(3)}$ is in contact with a cation and a configuration without resonance might have been expected. Secondly, the S–O bond length of 1·50 ± 0·01 Å is unusual, being significantly longer than the 1·44 Å normally found in sulphur acid anions, sulphones, etc., and shorter than the 1·6 Å found for S–O–X bonds in, for example,

potassium ethyl sulphate (Jarvis, *Acta Cryst.*, 1953, **6**, 327). The only accurate similar value reported is 1·493 Å in SO, but it is uncertain whether this refers to the ground state (Herzberg, "Spectra of Diatomic Molecules," Van Nostrand, New York, 1950, p. 573). Discussion of the significance of the present result is deferred for a later paper dealing with sulphur–oxygen compounds more generally.

Experimental

Crystals of sodium formaldehyde sulphoxylate dihydrate were grown from aqueous solution. Analysis showed them to contain 96·9% of $NaHSO_2.H{\cdot}CHO,2H_2O$.

The dimensions of the orthorhombic unit cell, measured by the method of Straumanis, are $a = 6{\cdot}78$, $b = 10{\cdot}835$, $c = 15{\cdot}97$ Å, all $\pm 0{\cdot}01$ Å, whence $U = 1173{\cdot}5$ Å^3. The axial ratios determined goniometrically (Osann, *Ber.*, 1905, **38**, 2290) were 0·8421 : 1 : 0·6783 compared with $2a : b : c = 0{\cdot}8487 : 1 : 0{\cdot}6784$ from the unit cell dimensions. The density calculated by assuming eight formula units (8×154) per unit cell is 1·73 g./c.c., in satisfactory agreement with 1·75 g./c.c. measured by the flotation method.

The space group *Pbca*-D_{2h}^{15} was uniquely determined from the systematic absences ($0kl$) when $k = 2n + 1$, ($h0l$) when $l = 2n + 1$, and ($hk0$) when $h = 2n + 1$. No molecular symmetry is required.

Sets of equi-inclination Weissenberg photographs were taken about the three principal axes using Ni-filtered Cu-K_α radiation. Intensity determination was carried out by the multiple-film technique, and the densities were compared visually with those on a calibration strip, made by exposing the film to the reflections from one plane for various lengths of time. Cochran's chart (*J. Sci. Instr.*, 1948, **25**, 253) was used for the application of the usual Lorentz and polarisation corrections. Approximate absolute values of F^2 for ($0kl$) reflections were obtained from the relative intensities by Wilson's statistical method (*Acta Cryst.*, 1949, **2**, 318). Values of F^2 for all (hkl) reflections were obtained by correlation, those for ($0kl$) being used as standard.

No absorption correction was made ($\mu = 52{\cdot}1$ cm.$^{-1}$); the crystals used were approximately cylindrical about the axis of rotation and 0·2 mm. in radius.

It is a pleasure to thank Professor E. G. Cox, F.R.S., for his helpful advice and criticism, Dr. D. W. J. Cruickshank and Miss D. E. Pilling for carrying out the calculations on the Manchester computer, and Dr. Furniss of Brotherton and Co. Ltd. for the analysis. Some of the equipment used was purchased with grants from the Royal Society and Imperial Chemical Industries Limited, and part of the cost of the computing work was borne by a grant from the D.S.I.R.

Department of Inorganic and Structural Chemistry,
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*Triterpenoids. Part XLI.** 12-*Oxo*-13α-*ursan*-3β-*yl Acetate.*

By G. G. Allan, F. S. Spring, and Robert Stevenson.

[Reprint Order No. 6232.]

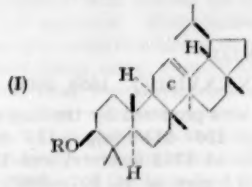
The products obtained by oxidation of α-amyrin esters with ozone or hydrogen peroxide, and hitherto considered to be esters of 12 : 13-epoxyursan-3β-ol (III; R = H), are now shown to be esters of an unstable ketone, 3β-hydroxy-13α-ursan-12-one (IV; R = H).

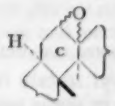
Oxidation of α-amyrin benzoate (I; R = Bz) † with hydrogen peroxide in acetic acid gives a product $C_{37}H_{54}O_3$, $[\alpha]_D$ +132°, which was considered to be a saturated ketone (Seymour, Sharples, and Spring, *J.*, 1939, 1075). Later, however, the corresponding acetate, $C_{32}H_{52}O_3$, $[\alpha]_D$ +114°, was obtained by oxidation of α-amyrin acetate (I; R = Ac) with either ozone (Ruzicka, Jeger, Redel, and Volli, *Helv. Chim. Acta*, 1945, **28**, 199) or

* Part XL, *J.*, 1955, 2616.

† The reasons for the assignment of the formula (I; R = H) to α-amyrin are given in Part XXXIX (*J.*, 1955, 2610) and the reason for the assignment of β-configuration to the 13-hydrogen in 12-oxoursan-3β-yl acetate (II) is to be found in Part XXXVI (*J.*, 1955, 2125).

hydrogen peroxide in acetic acid (McLean, Silverstone, and Spring. *J.*, 1951, 935) and, since this oxidation product is isomerised by mineral acid to 12-oxoursan-3β-yl acetate (II; R = Ac), $[\alpha]_D$ +11°, and carbonyl absorption was not observed in its ultraviolet absorption spectrum, it was considered to be 12 : 13-epoxyursan-3β-yl acetate (III; R = Ac). The structure of the related benzoate was revised to 12 : 13-epoxyursan-3β-yl benzoate (III; R = Bz), and a compound $C_{30}H_{50}O$, $[\alpha]_D$ +135°, obtained by oxidation of

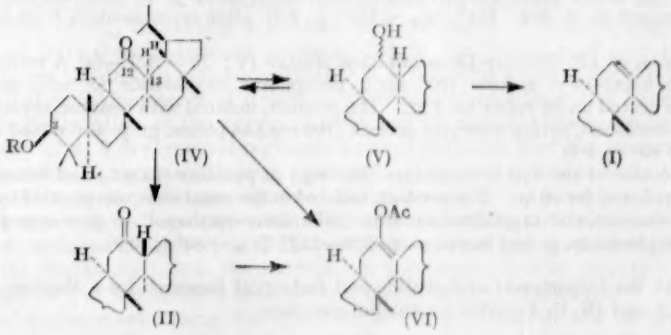




(III)

urs-12-ene with hydrogen peroxide was described as 12 : 13-epoxyursane. Treatment of the benzoate, $C_{37}H_{54}O_3$, and the compound $C_{30}H_{50}O$ with hydrochloric acid gave 12-oxoursan-3β-yl benzoate (II; R = Bz), $[\alpha]_D$ +25°, and ursan-12-one, $[\alpha]_D$ ±0°, respectively. During an investigation of some derivatives of ursolic acid, to be described in a later paper, the structure assigned to the acetate, $C_{32}H_{52}O_3$, $[\alpha]_D$ +114°, became suspect, and a re-examination of this compound was undertaken.

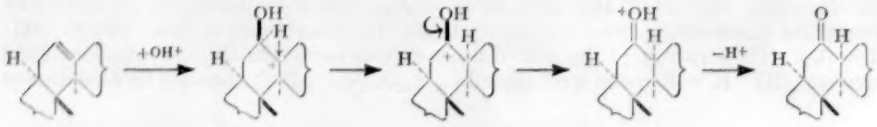
Treatment of the acetate $C_{32}H_{52}O_3$, $[\alpha]_D$ +114°, with lithium aluminium hydride yields a product, acetylation of which, at room temperature or at 100°, gives a diol monoacetate (V; R = Ac). Treatment of the diol monoacetate with phosphorus oxychloride in pyridine or with benzoyl chloride in pyridine yields α-amyrin acetate (I; R = Ac). Oxidation of the diol monoacetate with chromic acid at room temperature refurnishes the acetate $C_{32}H_{52}O_3$, $[\alpha]_D$ +114°, thus proving that the latter is a *ketone* and not an epoxide. This conclusion was confirmed by the infrared spectrum of the acetate which shows a well-defined carbonyl band at 1707 cm.$^{-1}$. The failure to detect low intensity ultraviolet carbonyl absorption in ethanol solution is probably due to the low concentrations employed (necessitated by sparing solubility); in high concentrations in chloroform solution, absorption at 2860° Å (ε 55) is apparent. The conversion of the acetate $C_{32}H_{52}O_3$, $[\alpha]_D$ +114°, into 12-oxoursan-3β-yl acetate (II; R = Ac) must therefore be represented as a simple inversion at $C_{(13)}$, *i.e.*, the former compound is 12-oxo-13α-ursan-3β-yl acetate (IV; R = Ac), and the related compounds obtained by oxidation of α-amyrin benzoate and urs-12-ene with hydrogen peroxide are 12-oxo-13α-ursan-3β-yl benzoate (IV; R = Bz)



and 13α-ursan-12-one, respectively. Treatment of 12-oxo-13α-ursan-3β-yl acetate with acetic anhydride and sodium acetate gives an enol acetate (VI; R = Ac) identical with that obtained by similar treatment of 12-oxoursan-3β-yl acetate (II; R = Ac).

The conversion of α-amyrin acetate into 12-oxo-13α-ursan-3β-yl acetate can be visualised

as frontal (β) attack by the per-acid, followed by a hydride shift on the rear side and proton elimination :



(I) (IV)

Experimental

For general instructions see Part XXXVIII (*J.*, 1955, 2606).

12-Oxo-13α-ursan-3β-yl acetate (IV; R = Ac) was prepared by treating α-amyrin acetate with hydrogen peroxide in acetic acid; it has m. p. 210—211°, $[\alpha]_D$ +115° (*c*, 0·9). Infrared absorption in carbon tetrachloride solution: bands at 1732 (acetate) and 1707 cm.$^{-1}$ (6-ring ketone). McLean, Silverstone, and Spring (*loc. cit.*) give m. p. 207—209°, $[\alpha]_D$ +114° and Ruzicka, Jeger, Redel, and Volli (*loc. cit.*) give m. p. 204—205°, $[\alpha]_D$ +139° for the compound described as "α-amyrin acetate oxide."

12-Oxoursan-3β-yl acetate (II; R = Ac), m. p. 280—282°, $[\alpha]_D$ +12° (*c*, 1·0), was prepared by treatment of 12-oxo-13α-ursan-3β-yl acetate with hydrochloric acid in acetic acid–chloroform, as described by McLean, Silverstone, and Spring (*loc. cit.*) who give m. p. 280—282°, $[\alpha]_D$ +11·4°.

3β : 12-*Diacetoxyurs*-12-*ene* (VI; R = Ac).—A mixture of 12-oxo-13α-ursan-3β-yl acetate (1·0 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (30 c.c.) was heated under reflux for 40 hr. The enol acetate (900 mg.), isolated in the usual way, crystallised from chloroform–methanol as needles, m. p. and mixed m. p. 257—259°, $[\alpha]_D$ +50° (*c*, 1·7). McLean, Silverstone, and Spring (*loc. cit.*) give m. p. 255—257°, $[\alpha]_D$ +49°, and Ruzicka, Jeger, Redel, and Volli (*loc. cit.*) give m. p. 256—257°, $[\alpha]_D$ +55°, for the enol acetate prepared from 12-oxoursan-3β-yl acetate.

12ξ-*Hydroxy*-13α-*ursan*-3β-*yl Acetate* (V; R = Ac).—Lithium aluminium hydride (1·5 g.) was added to a solution of 12-oxo-13α-ursan-3β-yl acetate (1·5 g.) in dry ether (750 c.c.), and the mixture kept overnight. The product, isolated in the usual way, was acetylated by pyridine and acetic anhydride at 100° for 15 min. Crystallisation of the product from chloroform–methanol yielded 12ξ-*hydroxy*-13α-*ursan*-3β-*yl acetate* (900 mg.) as plates, m. p. 234—235°, $[\alpha]_D$ +66° (*c*, 2·5) (Found: C, 78·7; H, 11·1. $C_{32}H_{54}O_3$ requires C, 79·0; H, 11·1%).

Oxidation of 12ξ-*Hydroxy*-13α-*ursan*-3β-*yl Acetate* (V; R = Ac) *with Chromic Acid.*—Chromium trioxide (75 mg.) in glacial acetic acid (15 c.c.) was added dropwise during 15 min. with stirring to a solution of 12ξ-hydroxy-13α-ursan-3β-yl acetate (500 mg.) in acetic acid (300 c.c.) at room temperature. After being kept overnight at room temperature the mixture was worked up in the usual way, to give 12-oxo-13α-ursan-3β-yl acetate (400 mg.) as plates, m. p. and mixed m. p. 209—211°, $[\alpha]_D$ +115° (*c*, 2·3), after crystallisation from chloroform–methanol.

Dehydration of 12ξ-*Hydroxy*-13α-*ursan*-3β-*yl Acetate* (V; R = Ac).—(*a*) A mixture of 12ξ-hydroxy-13α-ursan-3β-yl acetate (200 mg.), phosphorus oxychloride (5 c.c.), and pyridine (20 c.c.) was heated under reflux for 2 hr. The product, isolated with benzene, crystallised from chloroform–methanol, giving α-amyrin acetate (100 mg.) as plates, m. p. and mixed m. p. 225—227°, $[\alpha]_D$ +80° (*c*, 1·1).

(*b*) A solution of the diol monoacetate (500 mg.) in pyridine (15 c.c.) and benzoyl chloride (2 c.c.) was refluxed for 20 hr. The product, isolated in the usual way, was purified by chromatography on alumina and crystallisation from chloroform–methanol, to give α-amyrin acetate (160 mg.) as plates, m. p. and mixed m. p. 226—227°, $[\alpha]_D$ +80° (*c*, 0·9).

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to G. G. A.), and Dr. G. Eglinton for the infrared data.

The Royal Technical College, Glasgow. [*Received, March 14th*, 1955.]

The Constitution of a Modified Starch from Malted Barley.

By G. O. Aspinall, E. L. Hirst, and W. McArthur.

[Reprint Order No. 6394.]

The starch from malted barley has been isolated and shown to contain 26·0% of amylose. Methylation showed that the amylose consisted of unbranched chains containing an average of *ca.* 330 glucose residues. Methylation end-group assay, supported by β-amylolysis and periodate oxidation, indicated that the amylopectin contained the normal type of branched structure, but with one non-reducing terminal group per 18 ± 1 glucose residues. It is concluded that during the malting of barley the amylopectin has undergone enzymic attack causing shortening of the outer chains but with retention of the branched structure, while the amylose component has been relatively little degraded.

Structural investigations have recently been carried out on starches from a variety of sources. In this paper we report an examination of the starch from malted barley (a mixture of Plumage Archer and Spratt Archer varieties), carried out to determine the changes in structure of the starch during the malting process. The isolation was achieved without the use of reagents likely to cause degradation. The starch had an amylose content of 26·0%, a value significantly higher than that of the starch from the corresponding sample of barley and of the barley starch examined by McWilliam and Percival (*J.*, 1951, 2259). The most satisfactory separation of malted-barley amylopectin was achieved by using 20% aqueous pyridine saturated with butanol as the amylose precipitant (Higginbotham and Morrison, *Shirley Inst. Mem.*, 1948, **22**, 148). The amylopectin so obtained had an amylose content of not more than 0·5%. The amylose was isolated by fractionation of the starch with 15% aqueous pyridine (Whistler and Hilbert, *J. Amer. Chem. Soc.*, 1945, **67**, 1161), followed by successive reprecipitations as the butanol complex (Higginbotham and Morrison, *loc. cit.*).

Methylated amylopectin was prepared by standard methods and quantitative paper chromatography (Hirst, Hough, and Jones, *J.*, 1949, 928) of a small-scale hydrolysate showed the presence of tetra- (5·5%), tri- (86·1%), and di-*O*-methylglucose (8·4%). The mixture of methylated sugars obtained on hydrolysis of the methylated polysaccharide on a larger scale was fractionated by partition chromatography on cellulose, to give 2 : 3 : 4 : 6-tetra- (5·7%), 2 : 3 : 6-tri- (87·4%), and 2 : 3-di-*O*-methyl-D-glucose (4·3%), isolated as crystalline substances or as crystalline derivatives. In addition there was obtained a small fraction (2·6%) containing a mixture of 2 : 6- and 3 : 6-di-*O*-methylglucose. The quantity of tetra-*O*-methylglucose corresponded to the presence of one non-reducing terminal group per 18—19 glucose residues. It is doubtful whether the mixture of 2 : 6- and 3 : 6-di-*O*-methylglucose is of structural significance, since they may have arisen from incomplete methylation of the polysaccharide and by demethylation during hydrolysis. The quantity of 2 : 3-di-*O*-methyl-D-glucose isolated indicates that the majority, at least, of the interchain linkages were through position 6. The yield of formic acid from periodate oxidation of the amylopectin corresponded to one non-reducing group per 18 ± 1 glucose residues, a value in good agreement with that from the methylation data. Estimation of the glucose produced on hydrolysis of the periodate-oxidised polysaccharide indicated that 0·63% of the glucose residues in the amylopectin were unattacked by periodate. It follows that at least 88% of the linkages between unit chains were 1 : 6-linkages.

Further evidence concerning the structure of the amylopectin was obtained from its degradation by β-amylase, when in two experiments 44% and 47% of the molecule was converted into maltose. This value for the β-amylolysis of malt amylopectin is significantly lower than the values (52—62%) normally found for amylopectins (see Manners, *Quart. Rev.*, 1955, **9**, 73). As β-amylase only attacks the exterior chains of amylopectins, the enzymic degradation stopping at one or two glucose units from the inter-chain linkage,

it can be calculated that the β-limit dextrin had an average chain length of 9—10. A value of 8—9 residues for the chain length of the limit dextrin was obtained on periodate oxidation of the polysaccharide isolated after β-amylolysis. This is in close agreement with the values previously found for amylopectin β-limit dextrins (cf. Halsall, Hirst, Hough, and Jones, *J.*, 1949, 3200).

The malted-barley amylose was methylated, initially with diazomethane and subsequently with the usual reagents, and hydrolysis of the methylated polysaccharide gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (0·32%), 2 : 3 : 6-tri-*O*-methyl-D-glucose (98·0%), and a mixture of di-*O*-methylglucoses (1·6%). It is doubtful if the dimethyl sugars are of structural significance. The quantity of tetra-*O*-methylglucose corresponded to the presence of one non-reducing terminal group per 310 ± 20 glucose residues. A value of 330—345 for the average chain length of the amylose obtained from periodate oxidation experiments was in reasonable agreement with that from the methylation data. The malt amylose, therefore, consisted of an unbranched chain of *ca.* 330 glucose residues. It is interesting that this amylose is completely converted into maltose by β-amylase (the experiment was kindly carried out by Dr. D. J. Manners), and, therefore, does not contain the barrier to complete β-amylolysis found in some amyloses (Peat, Thomas, and Whelan, *J.*, 1952, 722).

Investigations were also carried out on the starch from the same sample of barley which had been used to prepare the malt. This barley starch had an amylose content of 22·6% and the amylopectin component had an average chain length of 26 glucose residues. β-Amylolysis of the amylopectin gave a 59% conversion into maltose, from which an average chain length of 10 can be calculated for the limit dextrin. A value of 9—10 glucose residues was obtained on periodate oxidation of the polysaccharide isolated after β-amylolysis of the barley amylopectin.

From these investigations the main structural features of the starch from malted barley emerge. The amylopectin has the type of branched structure that is now well established for this starch component. The average chain length (18 ± 1), however, is significantly shorter than that normally found for amylopectins and, in particular, is shorter than that found for the corresponding barley amylopectin (26 ± 1), a value in agreement with that previously determined by McWilliam and Percival (*loc. cit.*). It is apparent, therefore, that the exterior chains of the amylopectin have been partially removed by enzymic action during the malting of the barley. The chromatographic identification of glucose and maltose in the aqueous-ethanolic extract of the malted barley suggests that the action has been that of β-amylase in conjunction with maltase. On the other hand the isolation of a methylated amylopectin of high molecular weight indicates that there has been no appreciable α-amylolytic action causing scission of the interior chains during malting. An alternative interpretation that the amylopectin component is the product of complete breakdown and resynthesis is less likely in view of the similarity between the β-limit dextrins of the barley and the malted-barley starch. The apparent increase in the amylose content of the malt starch is fully accounted for by the loss of *ca.* 25% of the amylopectin component by shortening of the exterior chains, and it appears that the amylose has undergone relatively little degradation during malting, the polysaccharide isolated after fractionation being of a similar size to the barley amylose examined by McWilliam and Percival (*loc. cit.*). It is to be remembered, however, that the amylose examined may not be representative of all the amylose present in the malt starch, since only 55% of the total amount of this component present in the malt was isolated. Nevertheless any shorter-chain amyloses, which escaped precipitation during the fractionation, were of large enough molecular size to be estimated as amylose in the potentiometric iodine titration.

The general pattern of changes undergone by the starch in the malting process has now been established, but many problems remain unsolved. For instance, the present results do not show whether the degradation of the outer chains of the amylopectin has been completely random, or whether in parts of the macromolecule enzymic action has been carried to one or two glucose units from the inter-chain linkage (as in β-amylolysis) while in other parts of the molecule no degradation has occurred. Although relatively little breakdown of the amylose component has so far been detected, a detailed comparison of the

linear fractions from barley and from malted barley would be of value, since considerable changes in this component could occur before the achroic limit was reached.

Experimental

The following solvents were used to separate the sugars and their derivatives: (A) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3; top layer), (B) butan-1-ol–ethanol–water (4 : 1 : 5; top layer), and (C) benzene–ethanol–water (169 : 47 : 15; top layer). Blue values were determined by Hassid and McCready's method (*J. Amer. Chem. Soc.*, 1943, **65**, 1154) as modified by Bourne, Haworth, Macey, and Peat (*J.*, 1948, 924). Potentiometric determinations of amylose were kindly carried out by Mr. D. M. W. Anderson and Dr. C. T. Greenwood (see Anderson and Greenwood, *J.*, in the press).

Isolation of Starch from Malted Barley.—Malted barley (mixture of Plumage Archer and Spratt Archer varieties; 1·5 kg.) was lightly pounded to split open the husk, most of the husk was blown off with a jet of air, and the starch granules were separated from further fibrous material by passage through a suitable sieve. The starchy material was extracted for 3 hr. with boiling aqueous ethanol to inactivate enzymes and to remove soluble sugars. The ethanolic extract was concentrated, and chromatographic examination of the resulting syrup showed the presence of glucose, fructose, arabinose, and maltose. The inactivated malt was dried, and ground in a " Raymond " laboratory mill, and a suspension in ethanol was passed through a 40-mesh sieve to remove the residual fibre. The separated starch granules were stirred with cold water for 3 hr. to remove water-soluble carbohydrates, the aqueous extract was decanted, and the crude starch was dried with ethanol and ether. After exhaustive extraction with boiling 1 : 19 aqueous methanol to remove fats, crude starch (400 g.) was isolated. Examination under the microscope showed the starch granules to be ovoid to spherical in shape, and many of them appeared to be slightly ruptured.

Purification of Starch.—(a) *Treatment with butanol and toluene.* Crude starch (120 g.) was stirred overnight in 0·1% aqueous sodium hydrogen sulphite (5 l.). Removal of the solid at the centrifuge gave a lower layer containing the heavier starch granules, and a pale brown protein-rich upper layer. The upper layer was removed as completely as possible, the starch layer was subjected to the same treatment three more times, and the starch was freeze-dried. As the starch still contained protein (2·5%), a sample (4 g.) was stirred in water (200 c.c.), and the suspension was shaken with butanol before being allowed to settle. The brown precipitate, obtained at the butanol–water interface was removed, and the procedure was repeated once with butanol and three times with toluene. Starch A (2·3 g.) was isolated by freeze-drying (Found: N, 0·05%).

(b) *Extraction with chloral hydrate.* Crude starch (20 g.) was extracted by the method of Meyer and Bernfeld (*Helv. Chim. Acta*, 1940, **23**, 875) to give starch B (14·3 g.) (Found: N, 0·03%). The starch had a blue value of 0·368.

Examination of Starches.—Starch A had $[\alpha]_D^{18}$ +154° (*c*, 0·9 in N-NaOH) and $[\alpha]_D^{18}$ +178° (*c*, 0·7 in 30% $HClO_4$). Potentiometric titration showed the presence of 26·0% of amylose. Periodate oxidation of a sample of the starch as described by Brown, Halsall, Hirst, and Jones (*J.*, 1948, 27) gave formic acid corresponding to one terminal non-reducing group per 25 glucose residues. The value corresponded to a chain length of 19 glucose residues in the amylopectin fraction.

Starch B had $[\alpha]_D^{16}$ +159° (*c*, 1·1 in N-NaOH) and $[\alpha]_D^{16}$ +182° (*c*, 0·78 in 30% $HClO_4$). Hydrolysis of a sample gave only glucose (97·6%). Potentiometric titration showed the presence of 27·8% of amylose.

Fractionation of Starch A.—Starch A (12 g.) was fractionated by Higginbotham and Morrison's method (*Shirley Inst. Mem.*, 1948, **22**, 148) with 4 : 1 aqueous pyridine and butanol. The amylose complex was separated, washed with water saturated with butanol, dispersed in water, and freeze-dried, to give an amylose-rich fraction (3·8 g.). The amylopectin was precipitated by pouring the supernatant liquor from the fractionation into ethanol (2 vols.), and the precipitate was dispersed in water and freeze-dried to give amylopectin A (5·4 g.). The amylose-rich fraction was dispersed in water, refractionated seven times with butanol (Higginbotham and Morrison, *loc. cit.*), and isolated as before, to give amylose A (1·1 g.).

Examination of Starch Fractions.—*Amylopectin A.* This fraction had $[\alpha]_D^{18}$ +147° (*c*, 0·5 in N-NaOH) and $[\alpha]_D^{18}$ +166° (*c*, 0·5 in 30% $HClO_4$) (Found: N, 0·05%). Potentiometric titration showed the presence of 3·9% of amylose. Periodate oxidation of a sample gave formic acid corresponding to one terminal non-reducing group per 18 glucose residues.

Amylose A. This fraction had $[\alpha]_D^{18}$ +148° (*c*, 0·5 in N-NaOH) and $[\alpha]_D^{18}$ +198° (*c*, 0·7 in 30% $HClO_4$) (Found: N, 0·02%). Potentiometric titration showed that the amylose had a maximum iodine-binding power of 18·3%.

Large-scale Fractionation of Malted Barley Starch.—Preliminary fractionation of samples of the crude malted-barley starch showed that an amylose fraction with the highest blue value was obtained by fractionation of the starch with 85 : 15 water–pyridine (Whistler and Hilbert, *J. Amer. Chem. Soc.*, **1945**, **67**, 1161), and that an amylopectin fraction of low amylose content was obtained by fractionation using 4 : 1 aqueous pyridine saturated with butanol (Higginbotham and Morrison, *loc. cit.*).

Crude malted-barley starch (30 g.) was suspended in cold water (200 c.c.), and the suspension was added slowly with vigorous stirring to water (2 l.) and pyridine (450 c.c.) at 90°. The solution was maintained at this temperature for 2·5 hr. to ensure maximum dispersion of starch, cooled to 70°, centrifuged at 2000 r.p.m. to remove insoluble fibrous material, and heated again to 90°. The solution was transferred to a Dewar flask and allowed to cool slowly for 60 hr., during which the amylose–pyridine complex separated. The products from four fractionations were combined and refractionated with water saturated with butanol (twice at an amylose concentration of 0·5%, six times at 0·2%, and four times at 0·1% concentration). The final amylose–butanol complex was dispersed in water (150 c.c.) and freeze-dried, to give amylose B (11·1 g.; this represents *ca.* 55% of the amylose originally present in the crude starch).

Crude malted-barley starch (60 g.) was suspended in water (200 c.c.), and the suspension was slowly added with vigorous stirring to water (1800 c.c.) and pyridine (400 c.c.) at 90°. The paste was stirred at this temperature for 3 hr., subjected to 5 minutes' high-speed stirring in an "Ato-Mix" disperser, cooled to 70°, and centrifuged to remove fibrous material. The paste was heated again to 90°, butanol (*ca.* 400 c.c.) was added slowly to saturate the solution, and the solution was transferred to a Dewar flask and allowed to cool slowly for 60 hr. The amylose complex was separated at the centrifuge and the supernatant liquid was concentrated under reduced pressure to 1500 c.c. and poured into ethanol (4500 c.c.). The precipitated polysaccharide was washed several times with water saturated with butanol, dispersed in water, and freeze-dried. Two such fractionations gave amylopectin B (41 g.).

Examination of malted-barley amylopectin.

Amylopectin B had $[\alpha]_D^{16}$ +149° (*c*, 1·1 in N-NaOH) and $[\alpha]_D^{16}$ +170° (*c*, 0·72 in 30% $HClO_4$). Hydrolysis of a sample gave only glucose (96·0%). The amylopectin had a blue value of 0·085, and potentiometric titration showed the presence of 0·5% of amylose (average of two determinations).

Methylation of the Amylopectin.—Amylopectin (24 g.) was methylated twelve times with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature, and the product (24·4 g.; OMe, 43·0%) was fractionated in boiling chloroform–light petroleum (b. p. 60—80°) mixtures, to give a main fraction {20·7 g.; $[\alpha]_D^{15}$ +200° (*c*, 0·5 in $CHCl_3$); OMe, 43·2%}. Part of this fraction (6·0 g.) was methylated twice more with methyl iodide and silver oxide, to give methylated amylopectin {5·2 g.; $[\alpha]_D^{15}$ +200° (*c*, 0·5 in $CHCl_3$); OMe, 43·5%}, used in subsequent experiments. The methylated amylopectin had $\eta_{sp.}/c$, 2·21 (*c*, 0·4 in *m*-cresol), corresponding to an apparent *M* 320,000 (see Hirst and Young, *J.*, 1939, 1475).

Hydrolysis of Methylated Amylopectin and Separation of Methylated Sugars.—A sample of the methylated amylopectin (50 mg.) was hydrolysed successively with methanolic and aqueous hydrogen chloride, and, after neutralisation with silver carbonate, the hydrolysate was examined on the chromatogram. Quantitative estimation (Hirst, Hough, and Jones, *loc. cit.*) revealed the presence of 2 : 3 : 4 : 6-tetra-*O*-methyl- (R_G 1·0, 5·5%), 2 : 3 : 6-tri-*O*-methyl- (R_G 0·84, 86·1%), di-*O*-methyl- (R_G 0·65, 0·58, 8·4%), and traces of mono-*O*-methyl-glucose and glucose. This result indicated the presence of one non-reducing terminal group per 18—19 glucose residues.

Methylated amylopectin (3·32 g.) was hydrolysed successively with methanolic hydrogen chloride (200 c.c.; 1%) for 5 hr. and with hydrochloric acid (300 c.c.; 0·5N) for 5 hr. The hydrolysate was neutralised with silver carbonate and de-ionised with Amberlite resins IR-100 and IR-4B, and the solution was concentrated to a syrup (3·35 g.). The syrup was fractionated on cellulose (64·3 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3; later, 1 : 1) saturated with water, and butan-1-ol partly saturated with water, as eluants to give four fractions.

Fraction 1. The syrup (329 mg.) was examined on the chromatogram and showed only 2 : 3 : 4 : 6-tetra-*O*-methylglucose, but hypoiodite oxidation indicated only 49% of aldohexose.

A sample (10 mg.) was rehydrolysed and chromatographic examination of the hydrolysate showed that 2 : 3 : 6-tri-*O*-methylglucose was also present. The syrup (310 mg.) was rehydrolysed with hydrochloric acid (20 c.c.; 1%) on the water-bath for 5 hr. After neutralisation with silver carbonate, the resulting syrup (290 mg.) was fractionated on filter sheets, using solvent C, to give fractions 1*a* (105 mg.) and 1*b* (112 mg.). Fraction 1*a* crystallised and after two recrystallisations from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. (with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose) 86—88° and $[\alpha]_D^{18}$ +98° → +83° (equil.) (*c*, 0·4 in H_2O) (Found: C, 51·2; H, 8·5; OMe, 52·0. Calc. for $C_{10}H_{20}O_6$: C, 51·2; H, 8·5; OMe, 52·5%). The derived 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-glucosylamine had m. p. and mixed m. p. 136—138° (Found: N, 4·3; OMe, 39·4. Calc. for $C_{16}H_{25}O_5N$: N, 4·5; OMe, 39·9%). Fraction 1*b* crystallised and after two recrystallisations from dry ether had m. p. and mixed m. p. (with 2 : 3 : 6-tri-*O*-methyl-D-glucose) 115—117°, $[\alpha]_D^{18}$ +88° → +68° (equil.) (*c*, 0·4 in H_2O) and $[\alpha]_D^{18}$ +67° → −35° (10 hr., const.) (*c*, 0·4 in methanolic 2% hydrogen chloride) (Found: OMe, 41·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). From the above results the amount of tetra-*O*-methyl-D-glucose was calculated to be 160 ± 8 mg., corresponding to one non-reducing terminal group per 18—19 glucose residues.

Fraction 2. The syrup (2·31 g.) crystallised and after two recrystallisations from dry ether had m. p. and mixed m. p. (with 2 : 3 : 6-tri-*O*-methyl-D-glucose) 115—117°, $[\alpha]_D^{18}$ +90° → +66° (equil.) (*c*, 1·0 in H_2O) and $[\alpha]_D^{18}$ +67° → −34° (10 hr., const.) (*c*, 1·0 in methanolic 2% hydrogen chloride) (Found: OMe, 41·5. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction 3. Chromatographic examination of the syrup (160 mg.) showed the presence of 2 : 3 : 6-tri-*O*-methyl- and 2 : 3-di-*O*-methyl-glucose. Separation on filter sheets with solvent B gave fractions 3*a* (28 mg.) and 3*b* (95 mg.). Fraction 3*a* was identified as 2 : 3 : 6-tri-*O*-methyl-D-glucose, m. p. and mixed m. p. 114—116°. Fraction 3*b* was a syrup which did not crystallise, but was chromatographically homogeneous (R_G 0·64 in solvent B) and had $[\alpha]_D^{18}$ +106° → +68° (equil.) (*c*, 0·4 in H_2O) (Found: OMe, 29·2. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). The sugar was identified as 2 : 3-di-*O*-methyl-D-glucose by conversion into 2 : 3-di-*O*-methyl-D-gluconophenylhydrazide, m. p. 160—162° (Found: OMe, 19·2. Calc. for $C_{14}H_{22}O_6N_2$: OMe, 19·7%).

Fraction 4. The syrup (70 mg.), which did not crystallise, had $[\alpha]_D^{18}$ +74° → +58° (equil.) (*c*, 0·5 in H_2O) and $[\alpha]_D^{18}$ +60° → −10° (8 hr., const.) (*c*, 0·5 in methanolic hydrogen chloride) (Found: OMe, 29·0. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). Chromatographic examination suggested the presence of 2 : 6- and/or 3 : 6-di-*O*-methyl-D-glucose (R_G 0·58 in solvent B). The syrup (35 mg.) was converted into the methyl glycosides and treated with sodium metaperiodate by Bell's method (*J.*, 1948, 992). 0·53 Mole of periodate was consumed per $C_9H_{18}O_6$ unit, indicating the presence of 53% of 2 : 6-di-*O*-methyl-D-glucose in the fraction. After destruction of excess of periodate, the chloroform-soluble extract was hydrolysed and chromatographic examination showed a single sugar (R_G 0·59 in solvent B) corresponding to 3 : 6-di-*O*-methyl-D-glucose. Hypoiodite oxidation showed 14·5 mg. of the sugar to be present, corresponding to 41% of the fraction.

Determination of Glucose Residues in the Amylopectin unattacked by Periodate.—Amylopectin (0·985 g.) was dissolved in water (80 ml.) containing potassium chloride (5 g.), and 0·3M-sodium metaperiodate (30 ml.) was added. The mixture was shaken in the dark for 10 days. After removal of periodate and other ions the oxidised polysaccharide was dissolved in 0·2N-sodium hydroxide (30 ml.), and sodium borohydride (0·25 g.) was added. After being kept overnight the solution was neutralised with acetic acid, dialysed, and taken to dryness. The resulting polyol was hydrolysed and the glucose formed was estimated by quantitative paper chromatography. The quantity of glucose found (7·3 mg.) showed that 0·63% of the glucose residues in the amylopectin were unattacked by periodate.

β-*Amylolysis of the Amylopectin.*—Amylopectin (24·3 mg.) was incubated at 73° with 0·2M-acetate buffer (pH 4·6; 10 c.c.), distilled water (39 c.c.), and crystalline sweet-potato β-amylase solution (1 c.c.) (kindly supplied by Dr. D. J. Manners). Aliquot portions were removed at intervals for determination of reducing power (as maltose) by means of the Shaffer–Somogyi reagent 60 as modified by Hanes and Cattle (*Proc. Roy. Soc.*, 1938, *B*, **125**, 387). After 4 hr. the conversion into maltose was complete at 44%.

Isolation of Malted-barley Amylopectin β-*Limit Dextrin.*—Amylopectin (0·624 g.) was dissolved in water (305 c.c.), and 0·2M-acetate buffer (pH 4·6; 100 c.c.) and β-amylase solution [25 c.c.; prepared from barley flour by Northcote's method (*Biochem. J.*, 1953, **53**, 348)] were added. After incubation for 48 hr. at 37° the conversion into maltose was complete at 47%. The solution was boiled for 10 min. to inactivate the enzyme, and coagulated protein was removed

by filtration. The solution was dialysed for 2 days, and the dextrin was precipitated with ethanol, redissolved in water (50 c.c.), and freeze-dried (yield, 0·274 g.) (Found: N, 0·9%). The dextrin (0·244 g.) was dispersed in water (100 c.c.) and shaken for 1 hr. with butanol (100 c.c.). The brown layer formed at the interface was removed, and the dextrin was precipitated with ethanol, dispersed in water, and freeze-dried (yield, 0·208 g.) (Found: N, 0·05%). The dextrin had $[\alpha]_D^{18}$ +149° (*c*, 0·5 in N-NaOH). Periodate oxidation of a sample gave formic acid corresponding to one non-reducing group per 8—9 glucose residues.

Examination of malted-barley amylose.

Amylose B had $[\alpha]_D^{16}$ +200° (*c*, 0·5 in H_2O), $[\alpha]_D^{18}$ +143° (*c*, 0·5 in N-NaOH), and $[\alpha]_D^{18}$ +205° (*c*, 0·5 in 30% $HClO_4$), and a blue value of 1·25. Potentiometric titration showed that the amylose had a maximum iodine-binding power of 19·2%. Hydrolysis of a sample gave only glucose (95·0%).

Periodate oxidation of the amylose gave one mol. of formic acid per 110—115 glucose residues. If one assumes the release of two mols. of formic acid from the reducing end-group and one mol. from the non-reducing end-group, this value corresponded to a chain length of 330—345 glucose residues. Hydrolysis of the periodate-oxidised amylose showed that there were no unattacked glucose residues.

Methylation of the Amylose.—Malt amylose (7·5 g.) was partly methylated by being kept at 0° in an ethereal solution of diazomethane (cf. Hough and Jones, *Chem. and Ind.*, 1952, 380). When the ethereal solution became colourless it was removed by decantation and fresh ethereal diazomethane was added. After 34 weeks the partly methylated amylose was isolated (Found: OMe, 20·2%). The polysaccharide was then methylated five times with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature, and the product (7·56 g.; OMe, 44·2%) was fractionated in boiling chloroform–light petroleum (b. p. 60—80°) mixtures, to give a main fraction (6·17 g.), $[\alpha]_D^{17}$ +206° (*c*, 1·0 in $CHCl_3$), $\eta_{sp.}/c$, 0·82 (*c*, 0·4 in *m*-cresol) (OMe, 44·8%).

Hydrolysis of Methylated Amylose and Separation of Methylated Sugars.—A sample of the methylated amylose (50 mg.) was hydrolysed and chromatographic examination of the hydrolysate showed the presence of 2 : 3 : 6-tri-*O*-methylglucose together with small quantities of di-*O*-methylglucose. The major part of the methylated amylose (4·25 g.) was hydrolysed as described for methylated amylopectin, and the resulting mixture of sugars (4·21 g.) was fractionated on cellulose in the usual way to give three fractions.

Fraction 1. Chromatographic examination of the syrup (27 mg.) showed only 2 : 3 : 4 : 6-tetra-*O*-methylglucose, but hypoiodite oxidation indicated only 47% of aldohexose. A sample (1 mg.) was rehydrolysed and chromatographic examination of the hydrolysate showed that 2 : 3 : 6-tri-*O*-methylglucose was also present. The syrup (22 mg.) was rehydrolysed with 1% hydrochloric acid (10 c.c.) on the water-bath for 5 hr. After neutralisation with silver carbonate, the resulting syrup (21 mg.) was fractionated on filter sheets with solvent C, to give fractions 1*a* (10·5 mg.) and 1*b* (9 mg.). Fraction 1*a* crystallised and had m. p. and mixed m. p. (with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose) 78—80°. Fraction 1*b* which did not crystallise, had R_G 0·82 in solvent B, corresponding to 2 : 3 : 6-tri-*O*-methyl-D-glucose, but was not examined further. From the above results the amount of tetra-*O*-methyl-D-glucose was calculated to be 12·8 ± 0·4 mg., corresponding to one non-reducing terminal group per 310 ± 20 glucose residues.

Fraction 2. The syrup (3·58 g.) crystallised and after two recrystallisations from dry ether had m. p. and mixed m. p. (with 2 : 3 : 6-tri-*O*-methyl-D-glucose) 115—117°, $[\alpha]_D^{18}$ +94° → +70° (equil.) (*c*, 1·0 in H_2O) and $[\alpha]_D^{18}$ +63° → −34° (8 hr., const.) (*c*, 0·95 in methanolic 2% hydrogen chloride) (Found: OMe, 41·4. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction 3. The syrup (51 mg.), which did not crystallise, had $[\alpha]_D^{18}$ +58° → −11° (8 hr., const.) (*c*, 0·4 in methanolic 2% hydrogen chloride) (Found: OMe, 29·0. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). Chromatographic examination showed the presence of sugars corresponding to 2 : 3-di-*O*-methyl-D-glucose (R_G 0·59 in solvent B) and to 2 : 6- and/or 3 : 6-di-*O*-methyl-D-glucose (R_G 0·53). Quantitative determination (Hirst, Hough, and Jones, *loc. cit.*) indicated the presence of 7·5% of 2 : 3-di-*O*-methyl-D-glucose (4 mg.). Periodate oxidation of the derived methyl glycosides (Bell, *loc. cit.*) showed that 79% of the fraction was 2 : 6-di-*O*-methyl-D-glucose. The periodate-oxidised methyl glycosides were hydrolysed and chromatographic examination of the hydrolysate showed the presence of 2 : 3- and 3 : 6-di-*O*-methylglucose.

Examination of barley starch and barley amylopectin.

In the following experiments the barley used corresponded to that from which the malted barley examined above was derived (*i.e.*, a mixture of Plumage Archer and Spratt Archer varieties).

Isolation and Purification of Barley Starch.—Crude barley starch (52 g.) was prepared in a manner similar to that described for malted barley starch, and the purification was carried out as for malt starch A. The pure barley starch (5 g.) had $[\alpha]_D^{18}$ +154° (*c*, 1·0 in N-NaOH) (Found : N, 0·02%). Potentiometric titration showed the presence of 22·6% of amylose. Periodate oxidation of a sample of the starch gave formic acid corresponding to one terminal non-reducing group per 32 glucose residues. The value corresponded to a chain length of 24 glucose residues in the amylopectin fraction.

Preparation of Barley Amylopectin.—Barley amylopectin was prepared from crude barley starch as described for malt amylopectin B. The amylopectin had $[\alpha]_D^{18}$ +148° (*c*, 1·2 in N-NaOH) (Found : N, 0·05%). The formic acid produced on periodate oxidation corresponded to an average chain length of 26 glucose residues. Potentiometric iodine titration showed the presence of 0·70% of amylose.

β-Amylolysis of Barley Amylopectin and Isolation of the β-Limit Dextrin.—Barley amylopectin was incubated with barley β-amylase, and after 46 hr. the conversion into maltose was complete at 59%. The β-limit dextrin was isolated as described for the malt dextrin. Barley amylopectin β-limit dextrin had $[\alpha]_D^{18}$ +153° (*c*, 0·5 in N-NaOH) (Found : N, 0·04%). Periodate oxidation of a sample gave formic acid corresponding to an average chain length of 9—10 glucose residues.

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The Mechanism of the Ullmann Diaryl Synthesis.

By Harry E. Nursten.

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New results reported accord with the free-radical mechanism proposed by Rapson and Shuttleworth for this synthesis.

In the reaction of iodobenzene with copper in the presence of an excess of ethyl benzoate it was shown by Rapson and Shuttleworth (*Nature*, 1941, **147**, 675) that, apart from the expected diphenyl, small amounts of ethyl diphenyl-2- and -4-carboxylate had been formed. These had been converted into, and identified as, fluorenone and diphenyl-4-carboxylic acid respectively, the amounts isolated corresponding to 0·6 and 0·2% of the iodobenzene used (Shuttleworth, Thesis, Univ. of Cape Town). It was considered that the result provided evidence for the participation of free radicals in the Ullmann reaction. Fanta (*Chem. Rev.*, 1946, **38**, 139) preferred a mechanism consisting of nucleophilic attack at the carbon–halogen bond by copper with formation of an activated complex at the metal surface, and interaction of the activated complex and a second molecule of the aromatic halide. Bell and Morgan (*J.*, 1954, 1716), however, supported the free-radical mechanism as it is difficult to imagine the existence of a transition complex in the formation of sterically crowded diaryls from 2 : 6-disubstituted halogenobenzenes.

In order to decide whether the intermediate is an aryl radical or a carbanion, Ullmann syntheses were performed with three halogenonitrobenzenes in the presence of an excess of either resorcinol or catechol. Phenols, being acidic, readily give up a proton to carbanions, *i.e.*, their presence in the Ullmann reaction should lead to dehalogenation if carbanions are involved. Resorcinol and catechol would be expected to be about equally effective in this, resorcinol possibly a little more so than catechol, as their dissociation constants are

$3{\cdot}6 \times 10^{-10}$ and $3{\cdot}3 \times 10^{-10}$ at 18° respectively (Landolt–Börnstein, 5th Edn., 1923, Vol. II, pp. 1147, 1139). However, if the mechanism is homolytic, the presence of phenols would again lead to dehalogenation, but catechol would favour the formation of the dehalogenated product more than resorcinol, because, for example, catechol is far more efficient as an antioxidant than resorcinol (cf. Egloff, Morrell, Lowry, and Dryer, *Ind. Eng. Chem.*, 1932, **24**, 1375) and Fieser (*J. Amer. Chem. Soc.*, 1930, **52**, 5204) found the " critical oxidation potential " of resorcinol and catechol to be 1·043 and 0·742 v respectively at 25°.

The important fact established by this investigation is that the Ullmann reaction of *o*- and *p*-iodonitrobenzene and of *o*-bromonitrobenzene carried out in an excess of catechol yielded more of the dehalogenated product (nitrobenzene) than when performed in an excess of resorcinol (cf. Table). This supports a free-radical mechanism for the Ullmann diaryl synthesis as proposed by Rapson and Shuttleworth (*loc. cit.*). That radicals are involved must now be accepted as highly probable, even if it cannot be regarded as rigorously proved.

That dehalogenation has been observed in Ullmann reactions carried out in the presence of tetrahydronaphthalene (Hardacre and Perkin, *J.*, 1929, 180; Lesslie and Turner, *J.*, 1932, 281) can be understood on the basis of a radical mechanism, but Smith (*J. Amer. Chem. Soc.*, 1949, **71**, 2855) and Smith and Campanaro (*ibid.*, 1953, **75**, 3602) found that copper in the presence of benzoic acid is an effective dehalogenating agent for aromatic halogenonitro-compounds. If a radical mechanism were operative, benzoate radicals should be formed and these would decompose with evolution of carbon dioxide (cf. Waters, " The Chemistry of Free Radicals," Oxford Univ. Press, 2nd Edn., 1948, p. 166). Copper and benzoic acid when heated together for 20 min. at 201—208° did not give off carbon dioxide, but in the presence of *o*-iodonitrobenzene 2·6% of carbon dioxide (calc. on the weight of *o*-iodonitrobenzene employed) was obtained. In spite of the difficulties in interpreting heterogeneous reactions this result also points to a radical mechanism.

Addition	Temp.	Yield (%) of dinitrodiphenyl crude	Yield (%) of dinitrodiphenyl recryst.	Yield (%) of tribromoaniline	Increase (%) in insoluble matter
		o-Iodonitrobenzene.			
None	200—220°	88	82	*	*
Resorcinol	200—210	43	37	28	97
Catechol	200—210	40	29	49	102
		p-Iodonitrobenzene.			
None	190—210	144	*	*	38
None	210—220	91	32	*	88
None	240—260	78	*	*	98
None	254—287	97	*	*	101
Resorcinol	240—250	0	*	13	68
Catechol	225—237	0	*	38	121
		o-Bromonitrobenzene.			
None	210—220	96	85	0	84
Resorcinol	210—215	0	*	35	94
Catechol	205—216	4	2	66	111

Reaction time: 20 min. after the gradual addition of copper bronze had been completed.
* Not determined.

Experimental

Reactions were carried out in boiling tubes heated in a metal-bath, the temperatures recorded being internal and uncorrected. The thermometer served as stirrer and no attempt was made to exclude air except in the experiments with benzoic acid. Even at higher temperatures, the exposed part of the boiling tube was sufficient to obviate the need for a condenser. The usual procedure was as follows: the iodonitrobenzene (2 g.) was melted and mixed with resorcinol or catechol (4·4 g., 5 mol.), heated to the stated temperature, and copper bronze (from B.D.H. Ltd.; 2 g.) was added slowly at such a rate as to keep the temperature within the required limits. The reaction was completed by heating for 20 min. The product was cooled and water added. The solid (A) was filtered off and washed with boiling methyl alcohol (10 c.c.). The filtrate and washings were transferred to a distillation flask and, being oily, usually required methyl alcohol (10 c.c.) for rinsing. On distillation, nitrobenzene and possibly some unchanged

halogenonitrobenzene were collected in the distillate, which was reduced by heating with tin (2 g.) and hydrochloric acid (30 c.c.) for 3 hr. under reflux. Methyl alcohol was distilled off, then any aniline after the solution had been made alkaline. The yield of aniline was determined by precipitation as tribromoaniline and weighing. The filtrate from which nitrobenzene had been distilled was made alkaline and extracted with ether. The extract, when dried and evaporated, may yield some dinitrodiphenyl. The aqueous layer was acidified and continuously extracted with ether, the extract being evaporated to dryness as a check on the changes undergone by the phenol. The solid (A) was continuously extracted with benzene, the extract on evaporation yielding most of the dinitrodiphenyl formed. The residue, usually copper and copper halide only, was weighed, the increase in weight above 2 g. providing a useful indication of the extent to which reaction had occurred. This increase is recorded in the last column of the Table on the basis of the increase in weight expected if all the halogen had combined with the copper. The yield of crude dinitrodiphenyl recorded in the Table is the total obtained from both the benzene and the ether extract; as this may include unaltered halogenonitrobenzene and substances not volatile in steam, the yield on purification is also given. For *o*-bromonitrobenzene the amount used (1·62 g.) had been proportionally reduced. For experiments without addition, double quantities and the normal, simple procedure were employed.

o-*Iodonitrobenzene.*—When prepared from *o*-nitrobenzenediazonium chloride it was obtained in citron needles, m. p. 51—52° (from methyl alcohol). The reaction was carried out also in the presence of boiling tetralin (5 mol.) for 1 hr. at 200—208°, the yields obtained being crude dinitrodiphenyl 85%, tribromoaniline 11%, increase in insoluble matter 96%. No appreciable reaction occurred between *o*-iodonitrobenzene and catechol at 200—208° during 20 min.

p-*Iodonitrobenzene.*—Preparation from *p*-nitrobenzenediazonium chloride gave almost colourless needles, m. p. 173·5—174·8° (from chlorobenzene–alcohol). At lower temperatures much remains unchanged in the Ullmann reaction as can be seen from the small increase in insoluble matter and the apparently high yield of dinitrodiphenyl. From the complex product formed at higher temperatures, a small amount of a *substance* was obtained forming orange prisms, m. p. 312—312·5° (from chlorobenzene–alcohol) (Found: C, 62·9; H, 3·6; N, 12·5. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·5; N, 12·3%). On treating *p*-iodonitrobenzene (2 g.) with catechol (4·4 g.) for 20 min. at 230—241°, no tribromoaniline could be isolated in the usual manner, but a black amorphous powder (2·48 g.) was formed. This contains nitrogen and iodine and is insoluble or only slightly soluble in most solvents, but largely soluble in acetone and completely soluble in pyridine, giving brown solutions. In sulphuric acid it gives a dirty green-blue solution. The substance was not investigated further, but it is formed as a by-product in the Ullmann reaction in the presence of catechol. Similar compounds were formed in small amount in the other reactions in the presence of phenols. In the Ullmann reaction in the presence of resorcinol, more than 33% of *p*-iodonitrobenzene was recovered unchanged. In the reactions in the presence of resorcinol or catechol the figures quoted for the yield of tribromoaniline do not include tribromoaniline derived from unchanged *p*-iodonitrobenzene distilled together with the nitrobenzene.

o-*Bromonitrobenzene.*—For this compound comparison of the weight of tribromoaniline obtained with the amount of bromine required for the bromination (Wild, "Estimation of Organic Compounds," Cambridge Univ. Press, 1953, pp. 89, 180) enables one to determine the proportion of unchanged *o*-bromonitrobenzene present in the nitrobenzene of the steam-distillate. In this manner it was shown that in the straightforward Ullmann reaction the tribromoaniline isolated (2%) was derived from unchanged *o*-bromonitrobenzene, and that in the reactions in the presence of a phenol none of the tribromoaniline had been formed from unaltered starting material. Such a check is impossible in the experiments with iodo-compounds, as iodine is replaced during the reduction and the bromination, but the figures for the increase in insoluble matter are a good indication of the extent to which iodine is removed during the reaction proper.

Nitrobenzene.—Estimation *via* aniline and tribromoaniline gave 90% of the theoretical values. In control experiments it was found that catechol and copper bronze produce aniline from nitrobenzene, more reduction occurring at higher temperatures, but the addition of iodine suppresses the reduction almost entirely.

Reactions in the Presence of Benzoic Acid.—Nitrogen, purified by passage through soda-lime and sulphuric acid, was passed over the surface of the mixture heated in a boiling tube. The gases then passed through a condenser, a liquid-nitrogen trap, calcium chloride, soda-lime (*A*), calcium chloride (*B*), and soda-lime. The mixture was kept at 200—210° (internal) for 20 min. and the passage of gas was continued for a further 20 min. whilst cooling, the liquid nitrogen

being removed during the last 10 min. When a mixture of *o*-iodonitrobenzene (2 g.), copper bronze (2 g.), and benzoic acid ("AnalaR"; 4·9 g., 5 mol.) was taken, the increase in weight of (*A*) + (*B*) was 9·3 mg.; there was no increase in weight when a mixture of copper bronze and benzoic acid was heated alone. In the former case, a 75% yield of tribromoaniline was obtained, Smith and Campanaro (*loc. cit.*) recording a 53% yield of nitrobenzene from a similar reaction.

Most of this work was carried out during the tenure of a lectureship at the Nottingham and District Technical College.

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The Preparation and Stability of Alkyl Dichloroboronites.

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The preparation of a number of alkyl dichloroboronites, $BCl_2{\cdot}OR$, by reaction of boron trichloride with alcohols, borates or chloroboronates has been investigated. The primary alkyl esters are stable at 20°, the secondary at −80°. There are two causes of this instability: decomposition (to alkyl chloride or to olefin) and disproportionation [to BCl_3 and $BCl(OR)_2$]; and which of these reactions predominates depends on experimental conditions. A probable mechanism for the formation of alkyl chloride is based on the relative stability of dichloroboronites when R is varied, stereochemical features (optical activity and molecular rearrangements), and the influence of electrophilic catalysts.

In earlier papers (*J.*, 1951, 1020, 2545) we described experiments on alcohol (*sec.*-octyl, CHPhMe, Bu^n, Bu^i, Bu^t)–boron trichloride–borate systems, in the course of which alkyl dichloroboronites from primary (Bu^n and Bu^i), but not secondary or tertiary alcohols were isolated. The present paper is concerned with methods of preparation of dichloroboronites, stoicheiometries of their decomposition, and constitutional, stereochemical, and environmental factors influencing the decomposition; experiments are described. It deals with *n*- and *iso*-propyl, the four isomeric butyl, *neo*pentyl, 1 : 2-dimethylpropyl, 1 : 2 : 2-trimethylpropyl, *n*-octyl, and 1-methylheptyl systems.

Interaction between boron trichloride and any of these alcohols or their borates or chloroboronates, in the proportions indicated in equations (1)—(3), gave dichloroboronites quantitatively. As boron trichloride is difficult to handle, an excess of it was used and the residue was easily removed under reduced pressure after the reaction.

$$(1)\quad BCl_3 + ROH \longrightarrow BCl_2{\cdot}OR + HCl$$

$$(2)\quad 2BCl_3 + B(OR)_3 \longrightarrow 3BCl_2{\cdot}OR$$

$$(3)\quad BCl_3 + BCl(OR)_2 \longrightarrow 2BCl_2{\cdot}OR$$

The dichloroboronites could react further by decomposition to an alkyl halide (4), elimination, producing an olefin (5), or disproportionation (6):

$$(4)\quad 3BCl_2{\cdot}OR \longrightarrow B_2O_3 + BCl_3 + 3RCl$$

$$(5)\quad 3BCl_2{\cdot}OR \longrightarrow B_2O_3 + BCl_3 + 3HCl + 3Olefin$$

$$(6)\quad 2BCl_2{\cdot}OR \rightleftharpoons BCl_3 + BCl(OR)_2$$

Depending on experimental conditions either reaction (6) or reactions (4) and (5) together were observed, but the extent of the elimination (5) was not significant except with the *n*-octyl ester. When dichloroboronites were allowed to reflux (without heating in some cases), by reduction of pressure, boron trichloride (b. p. 12·5°/760 mm.) was gradually

removed and dialkyl chloroboronates remained (6). At atmospheric or higher pressures, under reflux, or in sealed tubes, decomposition (4) [with (5)] occurred. Distillation, whether under reduced or at atmospheric pressure, gave all the possible products. Only reaction (6) was reversible, whence the influence of pressure on the equilibrium (because of the high volatility of the trichloride) is clear.

Occurrence of reaction (4) or (6) has previously been regarded as characteristic of a particular type of branching, methyl, ethyl (Wiberg and Sütterlin, *Z. anorg. Chem.*, **1931**, **202**, 1, 22, 31), and *n*- and *iso*-butyl esters (Gerrard and Lappert, *loc. cit.*) undergoing reaction (4), and 2-chloroethyl (Edwards, Gerrard, and Lappert, *J.*, **1955**, 1470) and phenyl esters (Colclough, Gerrard, and Lappert, *ibid.*, p. 907) undergoing reaction (6); and only with 4-chlorobutyl dichloroboronite (Edwards *et al.*, *loc. cit.*) have both types of reaction been recognised.

Tris-1 : 2 : 2-trimethylbutyl borate is new; four others used by us have not hitherto been prepared by the reaction $3ROH + BCl_3 \longrightarrow B(OR)_3 + 3HCl$ (cf. Wiberg and Sütterlin, Gerrard and Lappert, *loc. cit.*) which gives them in nearly quantitative yields.

Factors governing reaction (4) were studied and a number of conclusions emerge.

(a) *Constitutional Factors.*—Changing the alkyl group, R, in the dichloroboronites showed that the stability is primary > secondary > tertiary. Tertiary dichloroboronites were not isolated (Gerrard and Lappert, *loc. cit.*). Evidence for the existence of secondary dichloroboronites at −80° was obtained (see also Gerrard and Lappert, *loc. cit.*), but they decomposed very rapidly at 20°. Primary alkyl dichloroboronites were stable at 20° for indefinite periods and the relative order of stabilities at 150° was estimated by heating weighed samples in sealed tubes and analysing the mixtures after arbitrary time intervals (dichloroboronites yield all their chlorine in ionic form on hydrolysis by cold water, whereas of the products of decomposition only the boron trichloride is so hydrolysed). The results are shown in Table 1.

TABLE 1.

R in RO·BCl_2	Pr^n	Bu^n	n-C_8H_{17}	Bu^i	Bu^t·CH_2
Decomp. (%) (½ hr.)	14	2	1	5·5	2
Decomp. (%) (1½ hr.)	46	24	15	62	29
Decomp. (%) (5 hr.)	93	100	95	92	81

(b) *Stereochemical Factors.*—Wagner–Meerwein rearrangement has already been shown to occur (Gerrard and Lappert, *loc. cit.*) in the decomposition of *iso*butyl dichloroboronite to *tert.*-butyl chloride. Other examples [Bu^t·$CH_2 \longrightarrow CMe_2Et$; $CHMePr^i \longrightarrow CMe_2Et$; (+)-$CHMeBu^t \longrightarrow CMe_2Pr^i$] are now given.

Reactions (1) and (2) with (+)-1-methylheptyl compounds have previously (Gerrard and Lappert, *loc. cit.*) been shown to give the configurationally inverted, but much racemised, 2-chloro-octane. It is now shown that these reactions involved 1-methyl heptyl dichloroboronite as an intermediate in that a stable 1 : 1 complex with pyridine has been isolated (see Lappert, *J.*, **1953**, 667, and Edwards *et al.*, *loc. cit.*, regarding pyridine–primary alkyl dichloroboronite adducts).

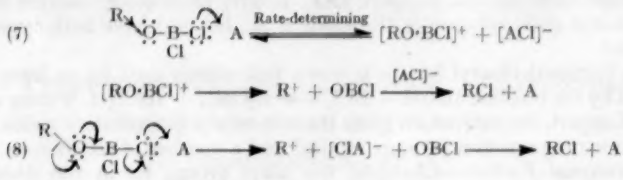
Both these stereochemical factors indicate a carbonium-ion intermediate in alkyl halide formation.

(c) *Environmental Factors.*—*n*-Butyl and *iso*butyl dichloroboronites are more stable than hitherto believed (Gerrard and Lappert, *loc. cit.*). The lower stability reported earlier is due to very small traces (<0·1%) of Lewis acid impurity, then present, which catalysed decomposition. Thus, it is now shown that the *n*-butyl ester is stable for 9 hr. at 100°, if prepared from rigorously purified boron trichloride. However, when a small quantity (1% by weight) of ferric or aluminium chloride was added decomposition was complete within ½ min. at room temperature. With *iso*butyl, *neo*pentyl, and 1-methylheptyl dichloroboronites, such catalytic decomposition did not affect the steric course of the reactions. Earlier work on the stability of dichloroboronites was repeated, but results for *sec.*- and *tert.*-butyl and *sec.*-octyl esters were substantially the same as already reported (Gerrard and Lappert, *loc. cit.*).

The Mechanism of Decomposition.—It is suggested that the mechanism of decomposition (4) of dichloroboronites involves a rate-determining initial fission of one B–Cl bond,

depending on two factors: the degree of electron release (+*I*) from the alkyl group, and the action of a second molecule of the ester, designated A in representations (7) and (8), which functions as an electrophilic catalyst and thus facilitates heterolysis of the B–Cl bond. Ferric and aluminium chloride (A) may also function in this way. If the alkyl group of the ester is bulky, the boron atom may be sterically shielded to some degree and thus its efficiency as an electrophilic catalyst may be decreased. This duality of mechanistic factors explains the observed influence of constitutional and environmental variations.

For later steps in the decomposition it is necessary to postulate that a carbonium cation be formed, either as a separate step (7) or by a process synchronous with B–Cl heterolysis (8).



Boron oxychloride which is here suggested as an intermediate, is supposed to decompose subsequently ($3BOCl \longrightarrow B_2O_3 + BCl_3$). A similar postulate was made by Wiberg and Sütterlin and by Gerrard and Lappert (*locc. cit.*), although the existence of an oxychloride was doubtful; but it appears now more probable in view of the isolation (Lappert, *loc. cit.*) of its stable 1 : 1 pyridine complex.

Experimental

Reagents.—*neo*Pentyl alcohol was prepared by Whitmore and Badertscher's method (*J. Amer. Chem. Soc.*, **1933**, **55**, 1559), 3-methylbutan-2-ol by Drake and Cooke's method (*Org. Synth.*, Coll. Vol. II, **1943**, p. 406), and 3 : 3-dimethylbutan-2-ol by reduction of pinacolone. The last-named alcohol was optically resolved by Pickard and Kenyon's method (*J.*, **1912**, **101**, 620). Boron trichloride was carefully redistilled before use.

Preparation of Trialkyl Borates.—Boron trichloride (1 mol.) in *n*-pentane was added (20—30 min.) to the alcohol (3 mols.) in *n*-pentane at −80°. The reaction was strongly exothermic. The mixture having been kept at −80° for 20 min., hydrogen chloride and solvent were removed at 10—15 mm. and the crude borate was distilled. Results are shown in Table 2. From 0·025

Table 2. *Alkyl borates.*

Alkyl	Yield (%)	B. p. (°/mm.)	n_D^{20}	d_4^{20}	Found (%) C	Found (%) H	Found (%) B	Calc. (%) C	Calc. (%) H	Calc. (%) B
Pr^n	96	176/760	1·3969	0·861	57·2	11·2	5·7	57·4	11·3	5·8
CH_2Bu^t	88	104/12	(m. p. 58—58·5°)		66·5	11·8	4·1	66·2	12·1	4·0
$CHMePr^i$	85	59—61/0·4	1·4080	0·844	66·5	12·1	4·0	66·2	12·1	4·0
$CHMeBu^t$	86	122/9	1·4151	0·841	68·5	12·3	3·3	68·8	12·4	3·2
$n\text{-}C_8H_{17}$	95	182—184/0·5	1·4377	0·855	72·8	12·9	2·7	72·4	12·9	2·7

to 0·10 mole of reagents was used, and the volume of solvent was 6 times that of the combined reactants. Reversal of addition (a more convenient procedure in view of the low b. p. of boron trichloride) gave substantially similar results. Physical constants are those obtained with redistilled samples.

Dichloroboronites by Reaction (1).—The alcohol (1 mol.) was added (20—30 min.) to boron trichloride (1 mol.) in absence of solvent at −80°. The mixture was allowed to warm to 20° and then kept at 20°/15—20 mm. (75 mm. for Pr^n) for 10 min. whilst mechanically shaken to remove hydrogen chloride and any excess of boron trichloride, which were collected in potassium hydroxide absorption tubes. Reagents were used in 0·01—0·05 mole amounts and the reverse order of addition gave substantially similar results. For primary esters the results are shown in Table 3 (for Me, Et, Bu^n, and Bu^i see Wiberg and Sütterlin, and Gerrard and Lappert, *locc. cit.*), but for secondary esters (for Bu^s see Gerrard and Lappert, *loc. cit.*) decomposition at 20° was rapid.

*iso*Propyl alcohol (1·03 g., 1 mol.) was added to boron trichloride (1·90 g., 1 mol.) at −80°,

After 5 min., dry nitrogen was passed for 15 min. through the mixture, still at −80°, and hydrogen chloride (0·60 g., 97%) was absorbed in traps containing potassium hydroxide. Hydrolysis of the residue in an enclosed system revealed that iso*propyl dichloroboronite* (Found: Cl, 49·4; B, 7·9. $C_3H_7OBCl_2$ requires Cl, 50·2; B, 7·7%) had been formed.

TABLE 3. *Alkyl dichloroboronites.*

Alkyl	Yield (%)	Yield of HCl (%)	n_D^{20}	d_4^{20}	Found (%) Cl	Found (%) B	Required (%) Cl	Required (%) B
Pr^n †	100	99	1·4094	1·138	49·6	7·6	50·2	7·7
CH_2Bu^t † *	98	97	1·4097	1·032	41·2	6·3	41·8	6·4
n-C_8H_{17}	99	98	1·4316	1·015	34·3	4·9	33·6	5·2

* Pentane used as solvent, as the alcohol is a solid.
† Purified by condensation (0·1 mm.) into a trap at −80°.

Dichloroboronites by Reaction (2).—The borate (1 mol.) was added (5 min.) to boron trichloride (slightly more than 2 mols.) at −80°. The mixture was warmed to 20° and excess of trichloride removed at 15—20 mm. (40 mm. for Pr^n) in 10 min.; the residue in the case of a primary alkyl compound was the dichloroboronite, but decomposition products (4) were obtained from secondary alkyl compounds. The results are shown in Table 4 (for Me, Et, Bu^n, Bu^i, and Bu^s

TABLE 4.

R in BCl_2·OR	Yield (%)	n_D^{20}	d_4^{20}	Found (%) Cl	Found (%) B
Pr^n	98	1·4110	1·140	49·6	7·6
CH_2Bu^t	98	1·4090	1·031	41·7	6·4
n-C_8H_7	99	1·4316	1·013	34·0	5·1

see Wiberg and Smedsrud, *Z. anorg. Chem.*, 1935, **225**, 204; Gerrard and Lappert, *loc. cit.*). Reversal of addition or the use of a solvent (*n*-pentane) made no significant difference.

Boron trichloride (4·13 g., 2 mols.) was added to tris-1-methylheptyl borate (7·00 g., 1 mol.) in *n*-pentane (30 c.c.) at −80° and the mixture was kept at −80° for a further 1 hr., whereafter pyridine (4·14 g., 3 mols.) in *n*-pentane (15 c.c.) was added. A white, pasty solid was formed instantly. After being kept for 3 hr. at 20° this was washed with more pentane and solvent then removed under reduced pressure. The precipitate (14·07 g.), which was treated with water, was a mixture of 1-methylheptyl dichloroboronite–pyridine (13·4 g., 87%) and pyridine–boron trichloride (Gerrard and Lappert, *Chem. and Ind.*, 1952, 53) (0·67 g.), m. p. 115°; the latter compound was insoluble; the former was hydrolysed, and gave analytical results corresponding to the 1 : 1 *complex* of dichloroboronite and pyridine (Found: Cl, 23·8; B, 3·7; C_5H_5N, 27·2. $C_{13}H_{22}ONCl_2B$ requires Cl, 24·3; B, 3·75; C_5H_5N, 27·2%).

Dichloroboronites by Reaction (3).—*n*- or *iso*-Butyl chloroboronate (Gerrard and Lappert, *J.*, 1951, 2545) (1 mol.) was added (5 min.) to boron trichloride (slightly more than 2 mols.) at −80°. The subsequent procedure was as described for reaction (2) and the results are shown in Table 5.

TABLE 5.

R in BCl_2·OR	Yield (%)	n_D^{20}	d_4^{20}	Found (%) Cl	Found (%) B	Calc. (%) Cl	Calc. (%) B
Bu^s	98	1·4161	1·079	45·7	7·0	45·8	7·0
Bu^i	99	1·4088	1·046	45·5	7·0	,,	,,

Decomposition (4) *and* (5) *of Dichloroboronites.*—The evidence for reaction (4) is shown in Table 6, which gives the data relating to yields and purity of end-products. These results are only some of many obtained in order to demonstrate that the stoicheiometry and the nature of the halide (*i.e.*, rearranged or not) was the same whether or not a catalyst was also present; conditions are not here stated as they were found to have no significant effect; in none of these experiments was reduced pressure used. 0·02—0·1 Mole of reagents was employed. The present results are additional to the earlier ones (Wiberg and Sütterlin, and Gerrard and Lappert, *locc. cit.*). Notes to Table 6 are: (*a*) These results are for sealed tube or catalysed reactions in open systems. (*b*) Octene (34%) was also formed, having b. p. 125—127°/760 mm., n_D^{20} 1·4157, d_4^{20} 0·723, which was further characterised as the dibromide, b. p. 108—109°/12 mm., n_D^{20} 1·4936, d_4^{20} 1·415. (*c*) When the optically active 3 : 3-dimethylbutan-2-ol, $[\alpha]_D^{20}$ +5·5°, was used the resulting halide was completely racemised. (*d*) These chlorides were also analysed for tertiary

alkyl chloride by hydrolysing weighed samples in dilute nitric acid in the cold (48 hr.) with subsequent Volhard titration. Blank experiments on authentic samples revealed that only a tertiary and not a secondary halide was thus hydrolysed. The results were 87% and 93% of *tert.*-pentyl chloride in the *neo*pentyl and 1 : 2-dimethylpropyl systems respectively and 74% of a *tert.*-hexyl chloride in the 1 : 2 : 2-trimethylpropyl system. (*e*) In these examples the dichloroboronites were not isolated at 20°.

TABLE 6.

	Yield of	Yield of	RCl				
R in BCl_2·OR	B_2O_3 (%)	BCl_3 (%)	Yield (%)	B. p. (°/mm.)	n_D^{20}	Found : Cl (%)	Calc. : Cl (%)
Pr^n	96	—	84	46—47	1·3864	44·8	45·3
Pr^i [e]	98	—	90	38—42	1·3782	45·0	45·3
CH_2Bu^t [a]	98	98	90	83—84	1·4045	32·7 [d]	33·2
CHMePr^i [a,e]	99	98	88	82—84	1·4042	32·8 [d]	33·2
CHMeBu^t [a,c,e] ...	98	96	85	108—110	1·4183	28·7 [d]	29·4
n-C_6H_{13} [b]	98	100	53	68/12	1·4311	23·4	23·9

For notes see text.

Disproportionation (6) *of Dichloroboronites.*—(a) n-*Octyl.* The dichloroboronite (9·52 g.) was heated (150°) under reflux at 15° for 7 hr. in order to allow boron trichloride to escape. On distillation at 0·5 mm. *n*-octyl chloride (1·00 g.), b. p. 40°/0·5 mm., and a middle fraction (1·00 g.), b. p. 128—132°/0·5 mm., n_D^{15} 1·4393 (Found : Cl, 13·9; B, 3·5%), were obtained. The final fraction (3·0 g., 50%) was tri-*n*-octyl borate, b. p. 178—182°/0·5 mm., n_D^{18} 1·4401 (Found : B, 3·2. Calc. for $C_{24}H_{51}O_3B$: B, 2·7%). The yield of borate is based on : $3BCl_2{\cdot}OR \longrightarrow B(OR)_3 + 2BCl_3$.

(b) neo*Pentyl.* The dichloroboronite (2·53 g.) was allowed to reflux for 4½ hr. at 20°/2 mm., a solid carbon dioxide–acetone cold-finger condenser and a mechanical shaker being employed. A residue (1·65 g., 100%) of *dineopentyl chloroboronate*, n_D^{16} 1·4125 (Found : Cl, 17·4; B, 5·2. $C_{10}H_{22}O_2ClB$ requires Cl, 16·1; B, 4·9%), remained. From an absorption tube at −80° containing pyridine, attached to the apparatus, pyridine–boron trichloride, m. p. 114° was isolated. The yield is based on equation (6).

(c) n-*Butyl.* As in (*b*), the dichloroboronite (5·47 g.) after 4½ hr. at 20°/14 mm., and then 3 hr. at 20°/0·2 mm., gave a residue (3·38 g.) of crude di-*n*-butyl chloroboronate (Gerrard and Lappert, *loc. cit.*) which was purified by removing the dichloroboronite by condensation (0·2 mm.). The residue (2·30 g.) was the pure chloroboronate (Found : Cl, 18·7; B, 5·8. Calc. for $C_8H_{18}O_2ClB$: Cl, 18·4; B, 5·65%).

Stability of Dichloroboronites.—In addition to information on p. 3085, catalytic acceleration of decomposition by aluminium or ferric chloride is shown in Table 7. The method of estimation

TABLE 7.

Time	Temp.	Catalyst	Catalyst (% w/w)	Decomp. (%)	Time	Temp.	Catalyst	Catalyst (% w/w)	Decomp. (%)
	n-*Butyl dichloroborinite*					neo*Pentyl dichloroboronite*			
<1 min.	20°	$FeCl_3$	1	100	5 hr.	17°	$AlCl_3$	0·7	20
9 hr.	100	—	—	<5	25 days	100	—	—	75
1 hr.	100	$FeCl_3$	0·2	98	4 days	17	$AlCl_3$	0·7	65
1 hr.	100	$AlCl_3$	0·2	96					

is by an analytical procedure as described on p. 3085, employing sealed samples (0·1—0·3 g.). The results were in satisfactory agreement with those of larger-scale experiments, wherein the extent of decomposition was estimated by isolation of the products. These decompositions were shown to be irreversible, because decomposed samples of pure dichloroboronites when kept at 20° for several days did not to any measurable extent re-form the esters.

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Acylation and Allied Reactions Catalysed by Strong Acids. Part XIV. Some Reactions of the α-Chlorodiphenylmethyl ($^+CPh_2Cl$) and p-Methoxytriphenylmethyl Cations.*

By H. Burton and G. W. H. Cheeseman.

[Reprint Order No. 6398.]

Diphenylmethylene dichloride (benzophenone chloride) with silver perchlorate or, more conveniently, aluminium chloride gives products showing the reactions of the α-chlorodiphenylmethyl cation, $^+CPh_2Cl$. Convenient methods of preparation of *p*-hydroxytriphenylmethanol and *p*-methoxytriphenylmethyl chloride are developed and various reactions of the *p*-methoxytriphenylmethyl cation are studied. The " rearrangement " of *p*-methoxytriphenylmethyl phenyl ether by hydrogen chloride gives 4-hydroxy-4′-methoxytetraphenylmethane.

In continuation of work described in Part IX (*J.*, 1953, 832) on the reactions of various di- and tri-arylmethyl cations we have investigated some reactions involving, in the first place, the α-chlorodiphenylmethyl cation. We have found that when silver perchlorate (1 mol.) is treated with diphenylmethylene chloride (1 mol.) in nitromethane there is immediate precipitation of silver chloride, and the resulting product reacts slowly with anisole at room temperature giving a good yield of *p*-methoxytriphenylmethyl chloride :

$$CPh_2Cl_2 + AgClO_4 \longrightarrow AgCl + {}^+CPh_2Cl\}ClO_4^-$$
$$^+CPh_2Cl\}ClO_4^- + PhOMe \longrightarrow p\text{-}OMe\cdot C_6H_4\cdot CPh_2Cl + HClO_4$$

The α-chlorodiphenylmethyl cation is, however, much less reactive than the diphenylmethyl cation (*loc. cit.*); thus it does not react with benzene under the conditions (2 hours at room temperature) which for the latter cation lead to triphenylmethane.

We have also found that aluminium chloride is an excellent catalyst for the " α-chlorodiphenylmethylation " of anisole and phenol. Diphenylmethylene dichloride (1 mol.) and aluminium chloride (1 mol.) in carbon disulphide form an insoluble complex which when treated with anisole (1 mol.) gives a good yield of *p*-methoxytriphenylmethyl chloride. The product similarly obtained from phenol (1 mol.) was hydrolysed directly to the alcohol. The methoxy-chloride can also be prepared conveniently by chromic oxide oxidation of *p*-methoxytriphenylmethane to the alcohol and subsequent treatment with acetyl chloride. Gomberg and Jickling's method (*J. Amer. Chem. Soc.*, 1915, **37**, 2578) of preparation of *p*-hydroxytriphenylmethanol is not suitable for its large-scale production. Ioffe and Khavin (*J. Gen. Chem. U.S.S.R.*, 1949, **19**, 903) have modified Gomberg and Jickling's method so that the formation of relatively large amounts of 4 : 4′-dihydroxytetraphenylmethane is avoided in experiments on a larger scale. We find that the action of phenol (1 mol.) with the diphenylmethylene dichloride–aluminium chloride complex is a much more convenient preparative method.

p-Hydroxy- and *p*-acetoxy-triphenylmethanol and fuchsone when treated with perchloric acid under suitable conditions all give *p*-hydroxytriphenylmethyl perchlorate, which is readily hydrolysed to *p*-hydroxytriphenylmethanol. The alcohol can also be obtained by direct hydration of fuchsone by perchloric acid in aqueous acetone (cf. Ioffe and Khavin, *loc. cit.* : Bistrzycki and Herbst, *Ber.*, 1903, **36**, 2335).

The ready preparation of *p*-methoxytriphenylmethyl chloride has enabled us to investigate various reactions, notably with phenol and *m*-dimethoxybenzene. It was found advantageous to carry out condensations with the chloride in presence of dry hydrogen chloride; reasonable yields of the tetra-arylmethanes were obtained. The use of *p*-methoxytriphenylmethyl perchlorate with phenol led to a mixture since, under the conditions used, extensive demethylation occurred.

We have also found that *p*-methoxytriphenylmethyl phenyl ether is " rearranged " to

* Part XIII, *J.*, 1955, 887.

4-hydroxy-4′-methoxytetraphenylmethane by dry hydrogen chloride at 95° (cf. van Alphen, *Rec. Trav. chim.*, 1927, **46**, 287). It is very probable that this so-called rearrangement involves, first, fission of the ether to phenol and *p*-methoxytriphenylmethyl chloride and then the interaction of these to give the tetra-arylmethane (cf. Hart and Cassis, *J. Amer. Chem. Soc.*, 1954, **76**, 1634).

Experimental

Diphenylmethylene dichloride (benzophenone chloride) was estimated by Andrews and Kaeding's method (*J. Amer. Chem. Soc.*, 1951, **73**, 1010).

Claisen's solution was prepared by dissolving potassium hydroxide (50 g.) in water (100 c.c.) and methanol (100 c.c.).

Reaction of "α-Chlorodiphenylmethyl Perchlorate" with Anisole.—Benzophenone chloride (11·9 g.; 93% pure) was added dropwise to a solution of silver perchlorate (10·4 g., 0·05 mole) and anisole (21·6 g., 0·20 mole) in nitromethane (50 c.c.); there was immediate precipitation of silver chloride. The dark red mixture was kept at room temperature for 5 days and then filtered. The filtrate was poured on crushed ice and extracted with ether, and the ethereal extracts were washed free from acid and dried (Na_2SO_4). Solvent and excess of anisole were removed by heating to 100°/0·1 mm.; the residue (14·6 g.) was heated under reflux with acetyl chloride (15 c.c.) in dry ether (30 c.c.). *p*-Methoxytriphenylmethyl chloride separated on cooling and was filtered off. Crystallisation from ether containing acetyl chloride gave the methoxychloride (11·1 g., 78%) as colourless prisms, m. p. 121—123°.

p-*Methoxytriphenylmethyl Chloride.*—(*a*) Powdered aluminium chloride (20·3 g., 0·15 mole) was added in portions to an ice-cooled solution of benzophenone chloride (35·8 g.; 93% pure) in anisole (16·2 g., 0·15 mole) and carbon disulphide (60 c.c.). After the initial reaction had moderated, the mixture was heated under reflux for 1 hr., then cooled, and crushed ice was added to decompose the dark red complex which had separated. Ether was added, and the organic layer separated, washed with dilute hydrochloric acid and water, and dried (Na_2SO_4). The residue (47·3 g.) after evaporation was heated under reflux with acetyl chloride (50 c.c.). *p*-Methoxytriphenylmethyl chloride separated on cooling and was filtered off in two crops, m. p. (mainly) 121—123°. The product was washed with ether and light petroleum and dried in a vacuum-desiccator over soda lime. The total yield was 39·3 g. (91%).

(*b*) *p*-Methoxytriphenylmethane (13·0 g., 0·04 mole; Burton and Cheeseman, *J.*, 1953, 832) was dissolved in acetic acid (100 c.c.), and the stirred solution kept at 60° while a solution of chromium trioxide (4·8 g., 0·048 mole) in water (3 c.c.) and acetic acid (30 c.c.) was added dropwise during 30 min. The mixture was kept at 60° for a further hour, then poured into water and extracted with ether. The combined ethereal extracts were washed with 2N-sodium hydroxide, dried (Na_2SO_4), and evaporated. The residue (13·5 g.) was converted into *p*-methoxytriphenylmethyl chloride (9·7 g., 66%), m. p. 117—121°, as described above. The mother-liquor contained benzophenone, isolated as its oxime, m. p. and mixed m. p. 141—142·5°.

p-*Hydroxytriphenylmethanol.*—Benzophenone chloride (47·4 g.; 97% pure) was added rapidly to a suspension of powdered aluminium chloride (26·8 g., 0·20 mole) in carbon disulphide (50 c.c.), whereupon a solid complex separated; a solution of phenol (18·8 g., 0·20 mole) in carbon disulphide (50 c.c.) was then added to the mixture. After the mixture had been heated under reflux for 4 hr., carbon disulphide was removed by distillation and the residual solid decomposed with water. The crude solid was filtered off, washed with water, and dissolved in N-sodium hydroxide (300 c.c.). The solution was shaken with ether to remove benzophenone, a current of air passed through the alkaline phase to remove dissolved ether, and *p*-hydroxytriphenylmethanol (51·5 g., 96%), m. p. (mainly) 156—159°, liberated with carbon dioxide. The alcohol was obtained as pale yellow prisms, m. p. 172°, by crystallisation from benzene (Found: C, 82·45; H, 5·8. Calc. for $C_{19}H_{16}O_2$: C, 82·6; H, 5·8%). It was converted into *p*-acetoxytriphenylmethanol (m. p. 136—139°) when heated under reflux with acetic anhydride and sodium acetate for 1 hr. (Gomberg and Jickling, *J. Amer. Chem. Soc.*, 1915, **37**, 2589). The reaction between benzophenone chloride and excess of phenol (*idem, ibid.*) was found to yield 47% of *p*-hydroxytriphenylmethanol and 31% of 4 : 4′-dihydroxytetraphenylmethane.

4 : 4′-Diacetoxytetraphenylmethane prepared by Mackenzie's method (*J.*, 1901, **79**, 1209) had m. p. 189—190° (Found: C, 79·6; H, 5·55. Calc. for $C_{29}H_{24}O_4$: C, 79·8; H, 5·55%) (Mackenzie gives m. p. 171°).

4 : 4′-*Dimethoxytetraphenylmethane*.—4 : 4′-Dihydroxytetraphenylmethane (7·0 g., 0·02 mole) in a solution of sodium hydroxide (2·5 g., 0·063 mole) in water (40 c.c.) and methanol (40 c.c.) was treated dropwise at 60° with stirring with methyl sulphate (6·3 g., 0·05 mole). The solid (5·8 g.), m. p. 156—163°, was collected after 3 hr. Successive crystallisations from acetic acid gave the pure *dimethoxy-compound*, m. p. 176—177° (Found : C, 85·2; H, 6·25. $C_{27}H_{24}O_2$ requires C, 85·2; H, 6·35%).

p-*Hydroxytriphenylmethyl Perchlorate*.—(*a*) 70% Perchloric acid (1·73 c.c.) was added to a solution of *p*-hydroxytriphenylmethanol (2·76 g.) in acetic acid (10 c.c.). Crimson needles of the perchlorate soon separated; these were filtered off, washed with acetic acid, and dried in a vacuum-desiccator (KOH). The salt (2·85 g., 80%) decomposed with bubbling at *ca.* 209—210° : the decomposition point was not strictly reproducible.

(*b*) The perchlorate was obtained in quantitative yield by the addition of an excess of 70% perchloric acid to a solution of fuchsone in acetic acid.

(*c*) Excess of a solution of perchloric acid in acetic acid (prepared from 70% perchloric acid and acetic anhydride) was added to *p*-acetoxytriphenylmethanol dissolved in acetic anhydride and acetic acid. Crimson needles of *p*-hydroxytriphenylmethyl perchlorate separated in 89% yield, decomposing at *ca.* 209—210° (undepressed when mixed with the perchlorate obtained by the methods described above) (Found : C, 63·3; H, 4·2. Calc. for $C_{19}H_{15}O_5Cl$: C, 63·6; H, 4·2%). The perchlorate was also obtained by adding 70% perchloric acid to a solution of *p*-acetoxytriphenylmethanol in acetic acid.

Hydrolysis of p-*Hydroxytriphenylmethyl Perchlorate*.—When water (10 c.c.) was added to a suspension of the perchlorate (1·0 g.) in acetone (10 c.c.), the undissolved solid went into solution and the mixture became much paler. Water and ether were added, the organic layer was separated and *p*-hydroxytriphenylmethanol (0·7 g., 90%), m. p. 156—158°, isolated *via* its sodium salt as described above.

Hydrolysis of Fuchsone.—Dilute perchloric acid (≡ 0·004 mole of $HClO_4$) was added to a solution of fuchsone (1·0 g., 0·004 mole) in acetone (20 c.c.). The mixture became pale yellow : water and ether were then added, the organic layer was separated, and *p*-hydroxytriphenylmethanol (1·0 g., 93%), m. p. 163—169°, isolated *via* its sodium salt as described above.

Fuchsone was recovered unchanged from a solution in acetone and ether which was shaken repeatedly with 2N-sodium hydroxide.

p-*Methoxytriphenylmethyl Perchlorate*.—70% Perchloric acid (4·5 c.c.) was added cautiously to a cooled solution of *p*-methoxytriphenylmethanol (6·8 g.) in acetic anhydride (20 c.c.). Crimson needles of the perchlorate soon separated; these were filtered off, washed with acetic acid, and dried in a vacuum-desiccator (KOH). The salt (7·9 g., 90%) had m. p. 192—193°.

Reaction of p-*Methoxytriphenylmethyl Perchlorate with Phenol*.—A solution of the perchlorate (3·73 g.) in phenol (10 g.) was kept at 100—110° for 6 days. The mixture was poured into sodium carbonate solution, excess of phenol removed by steam-distillation, and the residual oil extracted with ether. Evaporation of the dried ethereal extracts gave a crude solid (2·2 g.) which was partitioned between light petroleum (b. p. 60—80°) and Claisen's solution. *p*-Hydroxytriphenylmethanol (2·05 g., 74%) was liberated by carbon dioxide from the alkaline phase. The alcohol was converted into *p*-acetoxytriphenylmethanol, m. p. and mixed m. p. 136—139°, in 97% yield.

4-*Hydroxy*-4′-*methoxytetraphenylmethane*.—Dry hydrogen chloride was bubbled through a solution of *p*-methoxytriphenylmethyl chloride (3·08 g.) in phenol (10 g.) at 95° for 7 hr. The mixture was then poured into water, and excess of phenol removed by steam-distillation. The residual oil was partitioned between light petroleum (b. p. 60—80°) and Claisen's solution (20 c.c.). Evaporation of the petroleum layer gave an oil (0·5 g.), which yielded *p*-methoxytriphenylmethyl chloride, m. p. and mixed m. p. 121—123°, when heated under reflux with acetyl chloride. The alkaline layer was warmed to prevent crystallisation, and the crude product (2·8 g.) liberated with carbon dioxide. Crystallisation from ethanol (10 c.c.) gave 4-*hydroxy*-4′-*methoxytetraphenylmethane* (1·7 g., 46%), m. p. 189—192°, raised to 197—198° by crystallisation from ethanol and acetic acid (Found : C, 84·8; H, 5·9. $C_{26}H_{22}O_2$ requires C, 85·2; H, 6·05%). 4 : 4′-Dihydroxytetraphenylmethane and a smaller amount of the methoxyphenol were obtained from an experiment in which the reaction time was increased to 12 hr. Condensation occurred between *p*-methoxytriphenylmethanol and phenol in nitromethane in the presence of 70% perchloric acid. The yield of 4-hydroxy-4′-methoxytetraphenylmethane was 30% after 4 days at 110—120°.

2 : 4 : 4′-*Trimethoxytetraphenylmethane*.—Dry hydrogen chloride was bubbled through a solution of *p*-methoxytriphenylmethyl chloride (3·08 g.) in *m*-dimethoxybenzene (10 c.c.) at

95° for 12 hr. The mixture was then poured into water, and excess of dimethoxybenzene removed by steam-distillation. An ethereal solution of the non-volatile oil gave the *trimethoxy-compound* in two crops (total 0·63 g., 15%), m. p. 164—166°. The m. p. was raised to 168—169° by crystallisation from benzene–light petroleum (1 : 2) (Found : C, 82·2; H, 6·6. $C_{28}H_{24}O_3$ requires C, 81·9; H, 6·4%). The mother-liquor from the ether crystallisation gave *p*-methoxytriphenylmethyl chloride, m. p. and mixed m. p. 121—123°, when heated under reflux with acetyl chloride. No condensation occurred when *p*-methoxytriphenylmethyl chloride and *m*-dimethoxybenzene were heated alone at 95° for 12 hr.

"Rearrangement" of p-*Methoxytriphenylmethyl Phenyl Ether.*—Powdered *p*-methoxytriphenylmethyl chloride (6·17 g., 0·02 mole) was added to an ethereal solution of sodium phenoxide [from sodium (0·5 g.), phenol (10 g.) and ether (50 c.c.)] and the mixture heated under reflux for 2 hr. Water was added, the ethereal layer separated, and chloride precipitated as silver chloride from the aqueous layer (yield 2·85 g., 99%). The ethereal layer was washed repeatedly with 2N-sodium hydroxide, dried (Na_2SO_4), and evaporated. Dry hydrogen chloride was passed through the residual oil kept at 95°. The mixture became more and more viscous and solidified after *ca.* 4 hr. The solid dissolved when heated with Claisen's solution (20 c.c.); the crystals which separated on cooling were filtered off and redissolved in methanol–water (1 : 1). The crude phenol, m. p. 166—176°, was liberated with carbon dioxide. Crystallisation from ethanol (4 parts) gave 4-hydroxy-4′-methoxytetraphenylmethane (4·5 g.), m. p. 191—194° (yield 61%). Rearrangement of the ether in nitromethane solution, in the presence of 70% perchloric acid, gave the methoxy-phenol in 24% yield after 6 days at 110—120°.

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Some Physical Properties of Aliphatic Diphosphonates. Part I. Ethyl Esters.

By GENNADY M. KOSOLAPOFF.

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A family of esters of the general type $[CH_2]_x[PO(OEt)_2]_2$ was examined from $x = 1$ to $x = 5$ in respect to dielectric constant, index of refraction, density, and viscosity. The values of the dipole moments of these esters, calculated from the above data, showed good agreement with the data obtained previously for the monophosphonates.

As a result of the examination of some physical properties of various dialkyl alkylphosphonates, in which the variations of these properties were correlated with structure (Kosolapoff, *J.*, 1954, 3222; 1955, 2964; *J. Amer. Chem. Soc.*, 1954, **76**, 615), it was deemed advisable to examine a series of tetra-alkyl aliphatic diphosphonates, $(RO)_2P(O)\cdot[CH_2]_x\cdot P(O)(OR)_2$, in a similar manner. The tetraethyl esters were selected for the initial work because they are more readily purified than are the higher esters in this series, which boil at considerably higher temperatures. The esters examined were those in which x was 1—5.

The results of the measurements, which are recorded in the Table, showed some interesting points. The density–temperature plots of the five esters showed essentially the same slope, indicating a substantial independence of the degree of separation of the polar groups by the methylene units. The viscosity–temperature plots, however, showed a significant progression of differences. Thus, the esters with $x = 3$, 4, and 5 gave nearly identical viscosity–temperature curves, with a decided increase of the slopes at temperatures below 50°. The esters with $x = 1$ and 2 gave progressively lower viscosity values, indicating a considerable effect of the approach of the two polar groups to each other. Further, the decline in viscosity in the overall interval of temperature from 30° to 70° was much more pronounced for the esters with $x = 3$, 4, or 5 than with $x = 1$ or 2.

The values for the indices of refraction in this group of esters, with the density data, were used for the calculation of the molar refractions. In view of the fact that this had not been done previously with the diphosphonates, it is noteworthy that the value of 4·27 for the " phosphonate " type of phosphorus appears to apply very well indeed to the diphosphonates, as it does to the monophosphonates.

The values of the dielectric constants in this series, as expected, show a rise with the decreased separation of the polar groups by the methylene groups. The only relative anomaly is the high value found for the compound with $x = 3$, which is somewhat greater than that for the ester with $x = 2$.

From the data listed above it was possible to compute the dipole moments of the substances with the use of Onsager's equation (cf. Kosolapoff, *loc. cit.*). Owing to the structural complications in this family of esters, the use of Buckingham and Le Fèvre's formula (*J.*, 1952, 1932) was not feasible. The calculated dipole moments (see Table) were closely grouped, ranging only from 4·23 D for the methylene member to 4·38 D for the trimethylene member, the latter again being anomalous. The complete identity of the dipole moments for the esters with $x = 4$ and 5 is to be expected, possibilities of unrestricted rotation being common to both. The dipole moment of the methylene member was of a special interest. This value, 4·23 D, affords an independent check on the dipole-moment values calculated for the monophosphonates, particularly that for diethyl methylphosphonate. The latter, as reported earlier (Kosolapoff, *loc. cit.*), was found to be 3·33 D when calculated by Onsager's formula, or 3·11 D as the root-mean-square value of the two values (2·82 and 3·39 D, respectively) calculated, for the two extreme rotational possibilities of the side chains, by the Buckingham–Le Fèvre formula. If a not unreasonable assumption is made that the valency angle at the methylene group of the diphosphonate is close to the tetrahedral value, the calculated dipole moment of the diethyl phosphono-group is then equal to 4·23/1·15, or 3·68 D. With allowance for the polarity of the C–H link, necessary for such comparison, and equal probably to 0·3—0·4 D, the value of the moment of the polar part of the molecule agrees very well with the dipole moment of diethyl methylphosphonate as calculated by Onsager's equation, thus further justifying the use of this formula (and data obtained on the dielectric constant of pure liquids, as contrasted to solutions) for the esters of phosphorus acids. The rotational possibilities for the higher members in this family make any preliminary computations from their individual dipole moments unjustifiable.

Experimental

Preparation of Esters.—The esters were prepared by the conventional reaction of the organic dihalides with triethyl phosphite. When a 50% excess of triethyl phosphite was used over the calculated amount of 2 moles per mole of the dihalide, satisfactory yields of the diphosphonates were obtained, except in the case of the methylene member, as expected. The yields and the b. p.s of the esters are listed below :

x	1	2	3	4	5
B. p./mm.	127°/0·5	152°/0·5	163°/1	169°/0·7	178°/0·6
Yield (%)	26	61	72·5	61·6	62·3

It was intended originally to supplement this series by the corresponding tetra*iso*propyl esters. However, it was found that while tri*iso*propyl phosphite gives a generally better yield of the desired products, owing to the elimination of the side-reaction of formation of the phosphonate, $RP(O)(OR)_2$, the ethylene member of the series, $(Pr^iO)_2P(O)\cdot CH_2\cdot CH_2\cdot P(O)(OPr^i)_2$, was a rather high-melting solid (m. p. 52—53°); this unexpected result thus produced a gap in the proposed series, since the solid substance would not be suitable for the determination of dielectric constant and viscosity (at least below the m. p.). Incidentally, this ester is rather hygroscopic, becoming liquid after a short exposure to the air; a brief evacuation with a good pump at moderate temperature restores the solid state readily. In view of the above anomaly, physical measurements on this group of *iso*propyl esters were abandoned.

The dihalides employed in the preparations were the bromides, except for the methylene compound, which was the iodide. Tetramethylene bromide was prepared by hydrolytic cleavage of tetrahydrofuran by heating it with 48% hydrobromic acid–sulphuric acid; this

afforded a very clean reaction which in 1 hr. gave a 90·5% yield of the dibromide in one run and a 93% yield in another. The method often used for this preparation, *viz.*, reaction with dry hydrogen bromide, is relatively slow and produces much tar. Pentamethylene bromide was prepared similarly from tetrahydropyran in an 89% yield.

Physical constants of esters of type $[CH_2]_x[PO(OEt)_2]_2$.

x =	t	d_4^t	η (P)	x =	t	d_4^t	η (P)		n_D^{20}	$[M_R]$ found	$[M_R]$ calc.	ε^{20}	μ (D)
5	30°	1·0880	0·1549	2	30	1·1263	0·1100	x = 5	1·4443	84·04	83·97	11·070	4·28
	40	1·0790	0·1048		40	1·1169	0·0771	x = 4	1·4442	79·43	79·35	11·635	4·28
	50	1·0707	0·0726		50	1·1078	0·0570	x = 3	1·4422	74·77	74·73	12·696	4·38
	60	1·0620	0·0559		60	1·0987	0·0446	x = 2	1·4375	70·32	70·12	12·267	4·20
	70	1·0533	0·0433		70	1·0895	0·0338	x = 1	1·4261	65·17	65·49	12·768	4·23
4	30	1·1040	0·1548	1	30	1·1325	0·0982						
	40	1·0953	0·1039		40	1·1229	0·0675						
	50	1·0864	0·0724		50	1·1134	0·0497						
	60	1·0778	0·0555		60	1·1039	0·0387						
	70	1·0692	0·0428		70	1·0944	0·0306						
3	30	1·1186	0·1554										
	40	1·1097	0·1030										
	50	1·1008	0·0699										
	60	1·0917	0·0528										
	70	1·0825	0·0412										

The samples for the physical measurements on the diphosphonates were taken from the mid-portions of steadily-boiling specimens, distilled through an efficient ring-packed fractionating column. Freshly distilled specimens were employed.

The dielectric measurements were made as described previously (Kosolapoff, *J.*, 1954, 3222) at 30°. Viscometric determinations were made with the conventional Ostwald viscometer immersed in a thermostatically controlled oil-bath. Density measurements were made with a pyknometer.

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Some Derivatives of 2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine.*

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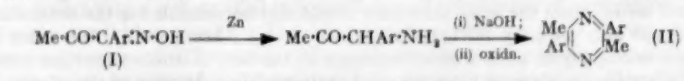
Condensation of diazonium salts with hydroxyiminoacetone affords derivatives of 1-hydroxyimino-1-phenylacetone which, on reduction followed by self-condensation, give aryl-substituted 2 : 5-dimethylpyrazines. Nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine and of its *NN'*-dioxide yields principally di-*m*-nitro-derivatives.

Condensation of diazonium salts with hydroxyiminoacetone (Borsche, *Ber.*, 1907, **40**, 737; Philipp, *Annalen*, 1936, **523**, 285) yields arylated derivatives of the latter (1-aryl-1-hydroxyiminoacetone) (I), which are convenient intermediates for syntheses of 3 : 6-



(II)

diaryl-2 : 5-dimethylpyrazines (II). This versatile method does not appear to have been described previously, although the less readily accessible α-hydroxyiminopropiophenones, Ar·CO·CMe:N·OH, have often been used for similar purposes (cf. Spring, *Ann. Reports*, 1945, **42**, 188).

Benzenediazonium chloride and derivatives bearing methyl, methoxy-, chloro-, methoxycarbonyl, and acetamido-substituents were condensed with hydroxyiminoacetone in aqueous sodium acetate in the presence of a cupric sulphate–sodium sulphite catalyst to give moderate to good yields of 1-hydroxyimino-1-phenylacetone derivatives. Diazotised 3-aminopyridine likewise gave 1-hydroxyimino-1-3′-pyridylacetone. When these compounds were reduced and the products subjected to self-condensation in the presence of oxidising agents, 3 : 6-diaryl-2 : 5-dimethylpyrazines were obtained.

As nitro-derivatives of 3 : 6-diaryl-2 : 5-dimethylpyrazines cannot be obtained from the nitroanilines by this method, the nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine was examined. Nitration with nitric–sulphuric acid gave 2 : 5-dimethyl-3 : 6-di-*m*-nitrophenylpyrazine, identified by reduction to the diamine and conversion by the Sandmeyer reaction into the dichloro-compound, which was identical with that prepared from *m*-chloroaniline. As the nitration of pyridine *N*-oxide is stated to occur almost exclusively in the 4-position (Hertog and Overhoff, *Rec. Trav. chim.*, 1950, **69**, 468) it was of interest to determine whether the nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine 1 : 4-dioxide would yield the di-*p*-nitro-derivative: such was not the case, however, the principal nitration product being again the di-*m*-nitrophenyl compound.

Experimental

Hydroxyiminoacetone.—The following modification of Charrier's method (*Gazzetta*, 1907, **37**, II, 145) was used. Ethyl acetoacetate (260 g.) was shaken with a cold solution of potassium hydroxide (130 g.) in water (1300 c.c.). After 24 hr. at 15—25°, sodium nitrite (161 g.) was added with stirring followed by dilute sulphuric acid (244 c.c. containing 122 c.c. of acid of *d* 1·84) at 0—8°. The solution was basified with aqueous 35% sodium hydroxide and shaken with benzene (100 c.c.). The aqueous layer was made just acid to Congo-red by addition of 50% sulphuric acid, and the product was extracted with ether (1 l.). Evaporation of the dried ($MgSO_4$) ethereal extract gave hydroxyiminoacetone (139 g., 80%), m. p. 65—67°.

Condensation of Diazonium Salts with Hydroxyiminoacetone.—(a) 1-*Hydroxyimino*-1-*phenylacetone.* A diazo-solution, prepared from aniline (93 g.), hydrochloric acid (230 c.c.; *d* 1·18), and water (200 c.c.) by treatment with sodium nitrite (69 g.) in water (100 c.c.) at 0—2°, was neutralised (Congo-red) with sodium acetate (88 g.; trihydrate) in water (140 c.c.). The diazonium solution was introduced below the surface of a solution of hydroxyiminoacetone (100 g.), sodium acetate (672 g.), cupric sulphate (25 g.), and sodium sulphite (4 g.; anhydrous) in water (680 c.c.) with stirring at 10—20°. After being stirred for 1 hr. at 20—25°, the solution was filtered and the residue extracted with hot N-sodium hydroxide (1600 c.c.). The extract was clarified (carbon) and the filtrate poured into hot acetic acid (150 c.c.) and water (150 c.c.) with stirring. The product (134 g., 82%) was collected and dried. After crystallisation from water, it had m. p. 165—166° (Found: N, 8·55. Calc. for $C_9H_9O_2N$: N, 8·6%).

1-p-*Carboxyphenyl*-1-*hydroxyiminoacetone.* A diazonium solution, prepared from ethyl *p*-aminobenzoate (165 g.), hydrochloric acid (230 c.c.; *d* 1·18), sodium nitrite (69 g.), water (300 c.c.), and ice (250 g.) in the usual manner, was condensed with hydroxyiminoacetone (100 g.) as described for benzenediazonium chloride. The crude product was boiled under reflux for 1 hr. with 2N-sodium hydroxide (1500 c.c.) and the extract was clarified (carbon) and filtered. Acidification of the filtrate with hydrochloric acid afforded crude 1-p-*carboxyphenyl*-1-*hydroxyiminoacetone* (145 g., 70%), m. p. 174—176°, which, after crystallisation from water (3300 c.c.), melted at 186° (Found: C, 57·5; H, 4·45; N, 6·75. $C_{10}H_9O_4N$ requires C, 57·95; H, 4·35; N, 6·75%).

The other *derivatives* of 1-hydroxyimino-1-phenylacetone shown in the Table were prepared similarly. [The m. p. (72°) given in the literature (D.R.-P. 294,159) for 4-amino-2-methoxyacetanilide is erroneous. A sample of the amine had m. p. 120—121° after crystallisation from butan-1-ol (Found: C, 60·1; H, 6·75; N, 15·55; OMe, 16·85. Calc. for $C_9H_{12}O_2N_2$: C, 60·0; H, 6·65; N, 15·55; OCH_3, 17·2%).]

1-*Hydroxyimino*-1-3′-*pyridylacetone.* A solution of 3-aminopyridine (23·5 g.) in hydrochloric acid (68 c.c.; *d* 1·18) and water (50 c.c.) was treated with sodium nitrite (17·5 g.) in water (25 c.c.) at 0°. The diazonium solution was condensed with hydroxyiminoacetone (25 g.) in water (215 c.c.) in the presence of sodium acetate (204 g.), cupric sulphate (6·25 g.), and sodium sulphite (1 g.; anhydrous) in the usual manner. The crude product was extracted

with boiling N-sodium hydroxide, the solution was clarified with carbon, and the product (24·5 g., 60%) reprecipitated by addition of acetic acid. Recrystallisation from methanol afforded long, silky needles of 1-*hydroxyimino*-1-3′-*pyridylacetone*, m. p. 201—202° (Found: C, 59·0; H, 5·2; N, 17·0. $C_8H_8O_2N_2$ requires C, 58·55; H, 4·9; N, 17·1%).

1-*Hydroxyimino*-1-*phenylacetone* derivatives.

R in Me·CO·CR:N·OH	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
o-C_6H_4Me	134—135°	$C_{10}H_{11}O_2N$	68·1	6·3	8·4	67·8	6·2	7·9
m-C_6H_4Cl	145	$C_9H_8O_2NCl$	—	—	7·0	—	—	7·1
p-C_6H_4Cl	177	$C_9H_8O_2NCl$ *	54·8	4·7	7·25	54·7	4·2	7·1
p-$NHAc{\cdot}C_6H_4$	187—188	$C_{11}H_{12}O_3N_2$	—	—	12·8	—	—	12·75
p-$NO_2{\cdot}C_6H_4$	202	$C_9H_8O_4N_2$	52·3	4·05	13·8	51·9	3·85	13·45
4 : 3-$NHAc{\cdot}C_6H_3(OMe)$	213—215 ‡	$C_{12}H_{14}O_4N_2$ †	57·4	5·8	11·55	57·6	5·6	11·2

* Found: Cl, 18·45. Reqd.: Cl, 17·95%. † Found: OMe, 12·7. Reqd.: OMe, 12·4%. ‡ With decomp.

Preparation of Pyrazine Derivatives.—2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine*. Zinc dust (80 g.) was added portionwise to a stirred solution of 1-hydroxyimino-1-phenylacetone (60 g.) in 5N-sodium hydroxide (600 c.c.) at 25—30°. The mixture was stirred for 2 hr., then diluted with water (600 c.c.) and filtered. The product was extracted with hot chloroform (500 c.c.), and air was bubbled through the extract for 15 min. After being dried ($MgSO_4$), the solution was evaporated and the residue was distilled at 1 mm. The gummy distillate was rubbed with a little ether, and the resulting solid crystallised from dilute acetic acid, giving 2 : 5-dimethyl-3 : 6-diphenylpyrazine (19·1 g., 40%), m. p. 126° (Kolb, *Annalen*, 1896, **291**, 267, gives m. p. 125—126°).

2 : 5-*Dimethyl*-3 : 6-*di*-o-*tolylpyrazine*, prepared similarly from 1-hydroxyimino-1-*o*-tolylacetone (36 g.), 5N-sodium hydroxide (320 c.c.), and zinc dust (43 g.), had m. p. 110—111° after recrystallisation from acetone, methanol, and dilute acetic acid (Found: C, 82·8; H, 6·8; N, 10·1. $C_{20}H_{20}N_2$ requires C, 83·3; H, 6·9; N, 9·7%).

2 : 5-*Di*-m-*chlorophenyl*-3 : 6-*dimethylpyrazine* was prepared similarly from 1-*m*-chlorophenyl-1-hydroxyiminoacetone. After crystallisation from acetic acid and from acetone the *compound* had m. p. 160° (Found: C, 66·0; H, 4·25; N, 8·8; Cl, 21·3. $C_{18}H_{14}N_2Cl_2$ requires C, 65·65; H, 4·25; N, 8·5; Cl, 21·6%).

2 : 5-*Di*-p-*chlorophenyl*-3 : 6-*dimethylpyrazine*, also prepared similarly, melted at 224—225° (Found: C, 65·65; H, 4·15; N, 8·35; Cl, 21·15%).

2 : 5-*Dimethyl*-3 : 6-*di*-3′-*pyridylpyrazine* was prepared from 1-hydroxyimino-1-3′-pyridylacetone (17·7 g.) and 5N-sodium hydroxide (185 c.c.) by treatment with zinc dust (25 g.) in the above manner. The crude product was extracted with chloroform and air was bubbled through the extract for 15 min. The chloroform was removed, the residue was dissolved in hot 2N-hydrochloric acid (100 c.c.), and the extract was clarified with carbon and basified with sodium hydroxide. The precipitated product (7·65 g., 54%) recrystallised from methanol or ethanol, after which the *compound* melted at 202—203° (Found: C, 73·1; H, 5·1; N, 21·35. $C_{16}H_{14}N_4$ requires C, 73·3; H, 5·25; N, 21·35%).

When boiled under reflux with methyl iodide (125 c.c.) for 16 hr., the compound (6·38 g.) yielded the *dimethiodide* (6·2 g.), m. p. 250° (decomp.) (Found: C, 39·25; H, 3·7; N, 10·0; I, 46·8. $C_{18}H_{20}N_4I_2$ requires C, 39·6; H, 3·65; N, 10·25; I, 46·5%).

2 : 5-*Di*-p-*carboxyphenyl*-3 : 6-*dimethylpyrazine*. A cooled (ice-bath) solution of 1-*p*-carboxyphenyl-1-hydroxyiminoacetone (104 g.) in 5N-sodium hydroxide (1 l.) was treated with zinc dust (106 g.), added portionwise below 30°. The mixture was diluted with water (1 l.) and filtered at 90—95°. Hydrochloric acid (*d* 1·18) was added until the filtrate was no longer alkaline to Brilliant-yellow; the alkalinity was just restored by addition of sodium carbonate, and the solution was filtered. A hot solution of mercuric chloride (280 g.) in water (800 c.c.) was added to the filtrate, which had been brought to pH 7—7·5 with acetic acid, at 40° with stirring. After 5 min., sodium carbonate was added until the solution was alkaline to Brilliant-yellow. The filtrate was acidified (Congo-red) with hydrochloric acid and the precipitate was collected and redissolved in hot, dilute sodium carbonate (1 l.). After filtration through kieselguhr, the solution was acidified with hydrochloric acid, and the crude product (55—60 g.) was collected and dried. After crystallisation from boiling pyridine, the *compound* (40—45 g., 50%) had

m. p. >320° (Found : C, 68·5; H, 4·75; N, 7·65. $C_{20}H_{16}O_4N_2$ requires C, 68·95; H, 4·6; N, 8·05%).

2 : 5-*Di*-p-*carbamoylphenyl*-3 : 6-*dimethylpyrazine*.—2 : 5-Di-*p*-carboxyphenyl-3 : 6-dimethylpyrazine (3·5 g.) was boiled under reflux with phosphorus pentachloride (4·5 g.) and phosphoryl chloride (30 c.c.) until completely dissolved. After removal of the latter by distillation under reduced pressure, the residue was warmed with an excess of aqueous ammonia (*d* 0·88) for 10 min. The *compound* (2·9 g.) was collected, washed with water, and dried; it had m. p. >340° (Found : N, 15·7. $C_{20}H_{18}O_2N_4$ requires N, 16·2%).

2 : 5-*Di*-p-*methoxycarbonylphenyl*-3 : 6-*dimethylpyrazine*.—2 : 5-Di-*p*-carboxyphenyl-3 : 6-dimethylpyrazine (60·9 g.) was boiled under reflux with thionyl chloride (260 c.c.) and pyridine (2 c.c.) until completely dissolved. After removal of excess of thionyl chloride by distillation, the residue was boiled under reflux with methanol (435 c.c.) for 3 hr. The solution was cooled and the ester was collected. After the crude product had been extracted with further methanol (100 c.c.), the residue (63·3 g., 96%) was crystallised from acetic acid and from dioxan. The pure *ester* (46·6 g., 71%) had m. p. 243—244° (Found : C, 70·15; H, 5·15; N, 7·65. $C_{22}H_{20}O_4N_2$ C, 70·2; H, 5·3; N, 7·45%).

2 : 5-*Di*-p-*aminophenyl*-3 : 6-*dimethylpyrazine*.—(*a*) 2 : 5-Di-*p*-carbamoylphenyl-3 : 6-dimethylpyrazine (2·8 g.) was added to sodium hypobromite prepared from sodium hydroxide (4 g.), water (35 c.c.), and bromine (1 c.c.). After being stirred for 5 min., the mixture was diluted with water (10 c.c.), heated on the steam-bath for 30 min., and cooled. The product was collected and dissolved in warm 2N-hydrochloric acid. The solution was clarified with carbon and added to a slight excess of boiling 2N-sodium hydroxide. The *diamine* (1·4 g., 60%) was collected and dried. It separated from 2-ethoxyethanol as pale yellow crystals, m. p. 277° (Found : N, 18·85. $C_{18}H_{18}N_4$ requires N, 19·3%).

(*b*) Zinc dust (40 g.) was added portionwise to a stirred solution of 1-*p*-acetamidophenyl-1-hydroxyiminoacetone (40 g.) in acetic acid (200 c.c.) and water (200 c.c.) at 60—75°. The solution was filtered at 55° and the filtrate was treated with ammonium chloride (80 g.) and excess of aqueous ammonia (*d* 0·88). The product was dissolved in hot acetic acid (400 c.c.) and the solution was filtered. The filtrate was diluted with water (1 l.) and basified with sodium hydroxide. The precipitate was collected and redissolved in hot acetic acid (400 c.c.) and the solution was diluted with water. Crystallisation of the product (14·3 g., 42%) from nitrobenzene afforded 2 : 5-*di*-p-*acetamidophenyl*-3 : 6-*dimethylpyrazine*, white needles, m. p. >300° (Found : C, 71·0; H, 5·8; N, 15·25. $C_{22}H_{22}O_2N_4$ requires C, 70·6; H, 5·9; N, 14·95%).

The acetyl compound (10·4 g.) was boiled under reflux with hydrochloric acid (100 c.c.; *d* 1·18) and water (100 c.c.) for 2 hr. The solution was cooled and basified with sodium hydroxide. The diamine (7·9 g.), after crystallisation from 2-ethoxyethanol, had m. p. and mixed m. p. 277°.

2 : 5-*Di*-(4-*amino*-3-*methoxyphenyl*)-3 : 6-*dimethylpyrazine*.—Zinc dust (141 g.) was added portionwise to a solution of 1-(4-acetamido-3-methoxyphenyl)-1-hydroxyiminoacetone (141 g.) in acetic acid (705 c.c.) and water (705 c.c.) with stirring at 60—75°. The mixture was filtered at 60° and the filtrate was treated with ammonium chloride (240 g.) and excess of aqueous ammonia (*d* 0·88). The product was collected and extracted with boiling acetic acid (1800 c.c.). The solution was filtered from tar, and the filtrate was diluted with water (5 l.). 2 : 5-*Di*-(4-*acetamido*-3-*methoxyphenyl*)-3 : 6-*dimethylpyrazine* (32·7 g., 27%) was collected; after crystallisation from acetic acid, it melted at 322° (Found : N, 12·95. $C_{24}H_{26}O_4N_4$ requires N, 12·9%).

The acetyl compound (32·5 g.) was boiled under reflux with 5N-hydrochloric acid (750 c.c.) for 1·5 hr.; the solution was basified with sodium hydroxide and the *amine* was collected. After crystallisation from 2-ethoxyethanol, it melted at 221—223° (Found : N, 15·5. $C_{20}H_{22}O_2N_4$ requires N, 16·0%).

Nitration of 2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine*.—A solution of 2 : 5-dimethyl-3 6-diphenylpyrazine (5·6 g.) in sulphuric acid (25 c.c.; *d* 1·84) was treated with a mixture of nitric acid (2·2 c.c.; *d* 1·5) and sulphuric acid (7 c.c.; *d* 1·84) at 5—10°. The temperature rose spontaneously to 40—42° and the mixture was stirred for a further 5 min. The solution was poured on ice, and the product collected. Crystallisation from pyridine (100 c.c.) afforded 2 : 5-*dimethyl*-3 : 6-*di*-m-*nitrophenylpyrazine* (4·72 g., 61%), m. p. 284—285°. After recrystallisation from pyridine, it had m. p. 285—286° (Found : C, 62·0; H, 4·05; N, 15·8. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0; N, 16·0%).

The nitro-compound (4·72 g.) was boiled under reflux with a solution of stannous chloride (30 g.) in hydrochloric acid (100 c.c.; *d* 1·18) until completely dissolved (2 hr.). The solution was cooled and the product collected. Treatment with concentrated aqueous sodium hydroxide

followed by continuous extraction with ethanol afforded 2 : 5-*di*-m-*aminophenyl*-3 : 6-*dimethylpyrazine* (2·7 g., 69%), m. p. 235—236° (from ethanol) (Found: C, 74·8; H, 6·15; N, 19·6. $C_{18}H_{18}N_4$ requires C, 74·5; H, 6·2; N, 19·3%).

The diamine (2·42 g.) was dissolved in water (80 c.c.) and hydrochloric acid (5 c.c.; *d* 1·18), and the solution was diazotised at 25° by 2N-sodium nitrite (8·3 c.c.). The diazonium solution was added to cuprous chloride (2·5 g.) in hydrochloric acid (75 c.c.; *d* 1·18), the solution diluted with water, and the product collected. After reprecipitation from acetic acid solution and crystallisation from acetic acid and from acetone, it had m. p. 160°, not depressed in admixture with a previous sample of 2 : 5-di-*m*-chlorophenyl-3 : 6-dimethylpyrazine (Found: C, 65·55; H, 4·0; N, 8·5; Cl, 21·1. Calc. for $C_{18}H_{14}N_2Cl_2$: C, 65·65; H, 4·25; N, 8·5; Cl, 21·6%).

2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine* 1 : 4-*Dioxide*.—2 : 5-Dimethyl-3 : 6-diphenylpyrazine (10·4 g.) was heated at 55—60° for 24 hr. with 30% hydrogen peroxide (18 c.c.) and acetic acid (90 c.c.). Further peroxide (46 c.c.) was added and heating was continued for a further 24 hr. The solution was diluted with water (1 l.) and basified with sodium hydroxide; the *dioxide* (10·12 g., 87%) was collected and dried. After recrystallisation from methanol or ethanol, it had m. p. 259—260° (Found: C, 73·85; H, 5·5; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·5%).

Nitration. A mixture of nitric acid (3 c.c.; *d* 1·5) and sulphuric acid (12 c.c.; *d* 1·84) was added dropwise to a solution of the dioxide (8·76 g.) in sulphuric acid (36 c.c.; *d* 1·84) with stirring at 5—10°. The solution was stirred for 0·5 hr., the temperature rising to 25°; it was then poured on ice and the product (9·25 g.) was collected. Crystallisation from acetic acid afforded 2 : 5-*dimethyl*-3 : 6-*di*-m-*nitrophenylpyrazine* 1 : 4-*dioxide* (5·5 g., 48%), m. p. *ca.* 300° (decomp.) (Found: C, 56·8; H, 3·9; N, 14·5. $C_{18}H_{14}O_6N_4$ requires C, 56·55; H, 3·65; N, 14·65%).

Reduction of this nitro-compound (5·5 g.) by boiling it under reflux with granulated tin (20 g.) and hydrochloric acid (100 c.c.; *d* 1·18) for 1 hr., basifying the solution with sodium hydroxide, and removing the tin with hydrogen sulphide gave 2 : 5-di-*m*-aminophenyl-3 : 6-dimethylpyrazine, m. p. and mixed m. p. 235—236°. Tetrazotisation of this product followed by the Sandmeyer reaction afforded 2 : 5-di-*m*-chlorophenyl-3 : 6-dimethylpyrazine, m. p. and mixed m. p. 160°.

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The Effect of Solvent on the Ionization of Organic Halides. Part III. The Extinction Coefficients of Carbonium Ions.*

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[Reprint Order No. 6368.]

When the ionization of triarylmethyl chlorides, RCl, was studied by measuring the carbonium-ion concentration spectrophotometrically, it was assumed that the extinction coefficient of the ion R^+ was the same for ion pairs $R^+Cl^-_{solv.}$ or free ions $R^+_{solv.} + Cl^-_{solv.}$ as in concentrated sulphuric acid. We have now established that the value of $\int D_\lambda d\lambda$ for a *m*-cresol solution containing R^+ ions is the same as for a concentrated sulphuric acid solution of the same R^+ ion concentration.

IN previous work (Bentley, A. G. Evans, and Halpern, *Trans. Faraday Soc.*, 1951, **47**, 711; Bentley and A. G. Evans, *J.*, 1952, 3468; A. G. Evans, Jones, and Osborne, *Trans. Faraday Soc.*, 1954, **50**, 16, 470; *J.*, 1954, 3803; A. G. Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1954, **50**, 378), the ionization of triarylmethyl chlorides in various solvents has been studied by measuring the concentration of the carbonium ions spectrophotometrically, assuming that the extinction coefficient of the R^+ ion (whether as an ion pair $R^+Cl^-_{solv.}$ or as free ions $R^+_{solv.} + Cl^-_{solv.}$) is the same as it is in concentrated sulphuric acid. We justified

* Part II, A. G. Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1955, **51**, 481.

this assumption by the fact that the spectrum of the R^+ ion in all the solvents used was so very similar in shape to that in concentrated sulphuric acid. We have now confirmed this assumption.

We chose a solvent of high ionizing power and a triarylmethyl chloride of marked ionizing tendency in the hope that under these conditions there would be complete ionization of the chloride. If this were attained, then our method of calculating the R^+ ion concentration should give 100% ionization. As a test for complete ionization, we have made use of the fact that, in general, a bromide RBr is more extensively ionized than is the corresponding chloride. Thus, when the latter is not completely ionized, the percentage ionization should increase on changing to the corresponding bromide. In contrast, when the chloride is completely ionized, the percentage ionization should not increase on changing to the bromide.

m-Cresol is a powerfully ionizing solvent, and in this solvent we find that the change from triphenylmethyl chloride to triphenylmethyl bromide gives a marked increase in optical density (for a given RHal concentration), showing incomplete ionization in the triphenylmethyl chloride solution. The change from tri-*p*-tolylmethyl chloride to tri-*p*-tolylmethyl bromide, on the other hand, causes no such increase, and this shows that both tri-*p*-tolylmethyl halides are completely ionized in these solutions. Calculation of the percentage ionization of tri-*p*-tolylmethyl halides in these solutions, by the $\int D_\lambda d\lambda$ method we have used previously, gave values of 100% within the experimental accuracy.

Materials.—*m*-Cresol, from Hopkin and Williams, was 98% pure. It was distilled, and the fraction boiling between 200° and 202° was collected. Further distillation had no effect on the results obtained. Triphenylmethyl bromide (m. p. 152°) and tri-*p*-tolylmethyl bromide [m. p. 170° (decomp.)] were obtained as white crystals by the action of redistilled acetyl bromide on the corresponding alcohol. The products were recrystallized, until colourless, from light petroleum (b. p. 40—60°) which had been dried over phosphoric oxide. Triphenylmethyl chloride and tri-*p*-tolylmethyl chloride were obtained as described by A. G. Evans, Jones, and Osborne (*Trans. Faraday Soc.*, 1954, **50**, 16).

m-Tolyl triphenylmethyl ether, m. p. 103°, was prepared from the sodium derivative of *m*-cresol and triphenylmethyl chloride (Schorigin, *Ber.*, 1926, **59**, 2506).

Procedure.—The solutions were examined as described in the papers quoted above.

Results

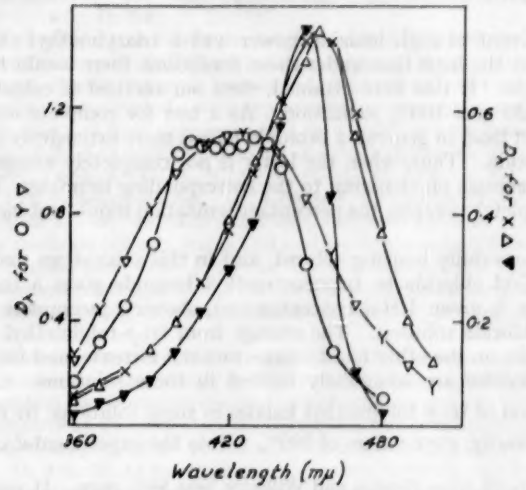
Spectra.—The spectra of the solutions of triarylmethyl halides in *m*-cresol are shown in Fig. 1. It is seen that the spectrum of the *m*-cresol solution of RHal is much broader than that of the R^+ ion in concentrated sulphuric acid. In the case of the triphenylmethyl halide, this broadening has resulted in the merging of the two peaks. For the tri-*p*-tolylmethyl halide, there is a slight peak shift. In spite of these small changes, however, it is quite clear that these spectra are those of the R^+ ion.

Dependence of R^+ *Ion Concentration on* RHal *Concentration.*—In Fig. 2 we show how the R^+Hal^- concentration (calculated as described below) depends on the concentration of un-ionized halide for triphenylmethyl halide, and on the concentration of the total halide for tri-*p*-tolylmethyl halide. It is seen that all the solutions give good straight lines.

Dependence of $[R^+Hal^-]/[RHal]$ *on Temperature.*—In Fig. 3 is shown the dependence of $\log_{10}[R^+Hal^-]/[RHal]$ on $1/T$ for the triphenylmethyl halides. These plots have not been corrected for the small volume change of the solvent with temperature (Int. Crit. Tab., **3**, 29). This volume change has been taken into account in calculating the ΔH°_1 values from these plots (see Table 2). (This correction is 0·2 kcal. mole^{-1}.) The slope of these plots does not vary with the total halide concentration. (It is seen that solutions of the halide having different optical densities at 21° give the same slope.)

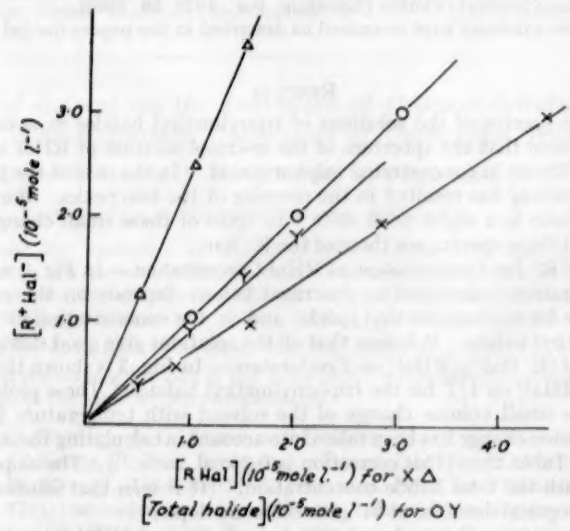
At high temperatures it was found that for solutions of RHal in *m*-cresol the optical density decreased with time. This is due to the reaction between the halide and the solvent which gives hydroxy-substituted tetraphenylmethane (Hantzsch, *Ber.*, 1921, **54**, 2595). This reaction is so slow at room temperature that it did not cause any change of

FIG. 1.



○ *Triphenylmethyl alcohol in* 98% H_2SO_4 ($2{\cdot}93 \times 10^{-6}$ *mole* $l.^{-1}$).
Y *Triphenylmethyl chloride in* m-*cresol at* 18° ($10{\cdot}5 \times 10^{-6}$ *mole* $l.^{-1}$).
▽ *Triphenylmethyl bromide in* m-*cresol at* 18° ($5{\cdot}6 \times 10^{-6}$ *mole* $l.^{-1}$).
▼ *Tri-p-tolylmethyl alcohol in* 98% H_2SO_4 ($0{\cdot}96 \times 10^{-6}$ *mole* $l.^{-1}$).
× *Tri-p-tolylmethyl chloride in* m-*cresol at* 18° ($1{\cdot}55 \times 10^{-6}$ *mole* $l.^{-1}$).
△ *Tri-p-tolylmethyl bromide in* m-*cresol at* 18° ($1{\cdot}71 \times 10^{-6}$ *mole* $l.^{-1}$).

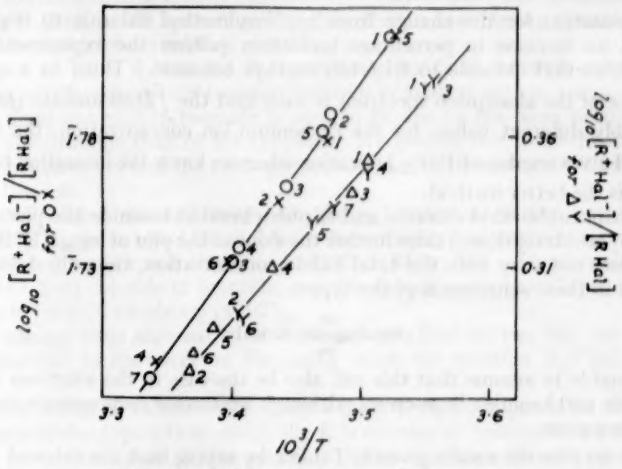
FIG. 2. *Solutions in* m-*cresol at* 18°.



× *Triphenylmethyl chloride.* ○ *Tri-p-tolylmethyl chloride.*
△ *Triphenylmethyl bromide.* Y *Tri-p-tolylmethyl bromide.*

optical density over the time of our concentration-dependence experiments. The temperature-dependence experiments were carried out over a temperature range of 9—25° and the optical density of the solution at any temperature within this range was reproducible over the time of the experiments. (See Fig. 3, in which the points are numbered to show the sequence in which the temperature was varied.)

FIG. 3. *The actual value of* D_{21}, *the optical density at 21°, as measured on the photomultiplier is given below for each solution. The value of* D_{21} *is directly proportional to the concentration of ions, and this is directly proportional to the halide concentration.*



× *Triphenylmethyl chloride in* m-*cresol,* $D_{21} = 0{\cdot}14$.
○ *Triphenylmethyl chloride in* m-*cresol,* $D_{21} = 0{\cdot}48$.
Y *Triphenylmethyl bromide in* m-*cresol,* $D_{21} = 0{\cdot}51$.
△ *Triphenylmethyl bromide in* m-*cresol,* $D_{21} = 0{\cdot}79$.

Table 1, column 3, gives the values of $[R^+Hal^-]$calculated for typical experiments on the assumption that $\int D_\lambda d\lambda$ is the same in these solutions as in concentrated sulphuric acid for the same concentration of carbonium ions. (This was the method used for calculating

TABLE 1.

	[Total halide] (10^{-5} mole $l.^{-1}$)	$[R^+Hal^-]$ (10^{-5} g.-ion $l.^{-1}$)	Ionization (%)
Triphenylmethyl chloride	4·91	1·75	36 ± 4
Triphenylmethyl bromide	7·50	5·10	68 ± 7
Tri-*p*-tolylmethyl chloride	0·995	1·00	100 ± 10
Tri-*p*-tolylmethyl bromide	0·99	0·899	91 ± 10

$[R^+Hal^-]$ in Figs. 2 and 3.) Using these values, we have calculated the percentage ionization in the various solutions (see column 4); these are reproducible to the limits given. For triphenylmethyl halides, where the change from chloride to bromide produces a two-fold increase in the percentage ionization, it is seen that the calculated percentage ionization is much less than 100%. For tri-*p*-tolylmethyl halides, where the change from chloride to bromide causes no appreciable variation in percentage ionization, the calculated percentage ionization is 100%, within the experimental accuracy. This establishes that our method of calculating the concentration of carbonium ions is valid.

If we calculate the carbonium-ion concentration by the alternative assumption that $(D_\lambda)_{max.}$ is the same in these solutions as in concentrated sulphuric acid for the same concentration of ions, we obtain the following values for the percentage ionization at the total halide concentration given in parentheses: triphenylmethyl chloride ($4{\cdot}91 \times 10^{-5}$ mole/l.)

30%; triphenylmethyl bromide ($7{\cdot}50 \times 10^{-5}$ mole/l.) 55%; tri-*p*-tolylmethyl chloride ($0{\cdot}995 \times 10^{-5}$ mole/l.) 63%; tri-*p*-tolylmethyl bromide ($0{\cdot}99 \times 10^{-5}$ mole/l.) 55%. These values are smaller than those calculated by the $\int D_\lambda d\lambda$ method. This is the first solvent we have studied in which these two methods give appreciably different results, and this difference arises because the carbonium-ion spectrum is so much broader in *m*-cresol than it is in concentrated sulphuric acid, and because the extent of ionization in this solvent is so high. Although these values are smaller than those obtained by the $\int D_\lambda d\lambda$ method, they show the same features, that is, a marked increase (two-fold) in percentage ionization for the change from triphenylmethyl chloride to triphenylmethyl bromide, and no increase in percentage ionization (within the experimental accuracy) from tri-*p*-tolylmethyl chloride to tri-*p*-tolylmethyl bromide. Thus, in a case like this, when the shape of the absorption spectrum is such that the $\int D_\lambda d\lambda$ and the $(D_\lambda)_{max.}$ method give appreciably different values for the carbonium-ion concentration, the fact that the $\int D_\lambda d\lambda$ method gives a value of 100% ionization when we know the ionization to be complete shows that it is the better method.

Since for triphenylmethyl chloride and triphenylmethyl bromide the plots of $[R^+Hal^-]$ against [RHal] are straight, and since further the slope of the plot of $\log_{10}([R^+Hal^-]/[RHal])$ against $1/T$ does not vary with the total halide concentration, the only detectable equilibrium present in these solutions is of the type:

$$RHal \underset{(b)}{\overset{(a)}{\rightleftharpoons}} R^+Hal^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is reasonable to assume that this will also be the case in the solutions of tri-*p*-tolylmethyl chloride and bromide in *m*-cresol, although we cannot demonstrate this since there is complete ionization.

We can summarize the results given in Table 1 by saying that the value of $\int D_\lambda d\lambda$ for the carbonium ion when it is present in $R^+Hal^-_{solv.}$ ion pairs in *m*-cresol is the same, within experimental error, as when it exists in the absence of ion pairs in concentrated sulphuric acid. Thus this very great change in environment does not affect the light absorption of the carbonium ion appreciably.

In Table 2 are given the values of the thermodynamic constants for equilibrium (1) obtained from the results given in Figs. 2 and 3 in the way described in our earlier papers. We estimate the accuracy of ΔG°_{1a} to be within $\pm 0{\cdot}1$ and $\pm 0{\cdot}2$ kcal. mole^{-1} for triphenylmethyl chloride and triphenylmethyl bromide respectively, and the accuracy of ΔH°_{1a} to be within $\pm 0{\cdot}2$ kcal. mole^{-1} for both halides. The corresponding thermodynamic constants cannot be given for the tri-*p*-tolylmethyl halides since, for these halides, there is complete ionization within experimental accuracy. From the results we see that *m*-cresol is a most powerful ionizing solvent. Comparing the values obtained at 20° for triphenylmethyl chloride in nitromethane ($K_1 = 4{\cdot}4 \times 10^{-4}$, $\Delta G^\circ_{1a} = 4{\cdot}5$ kcal. mole^{-1}, $\Delta H^\circ_{1a} = 1{\cdot}4$ kcal. mole^{-1}, and $\Delta S^\circ_{1a} = -10{\cdot}5$ cal. deg.$^{-1}$ mole^{-1} (A. G. Evans, Bentley, and Halpern; A. G. Evans, Jones, and Osborne, *locc. cit.*) with those given in Table 2 for *m*-cresol, we see

TABLE 2.

	K_1 (18°)	ΔG°_{1a} (18°) (kcal. mole^{-1})	ΔH°_{1a} (kcal. mole^{-1})	ΔS°_{1a} (cal. deg.$^{-1}$ mole^{-1})
Triphenylmethyl chloride ...	0·56	0·34	−3·0	−11·5
Triphenylmethyl bromide ...	2·12	−0·43	−2·4	− 6·9

that the change from nitromethane to *m*-cresol gives a 1000-fold increase in K_1, the equilibrium constant of reaction (1). This marked increase in the degree of ionization corresponds to a decrease in ΔG°_{1a} of 4·16 kcal. mole^{-1}, and this involves ΔH°_{1a} becoming more negative by 4·4 kcal. mole^{-1} and ΔS°_{1a} remaining unchanged. Thus the entropy of ionization in *m*-cresol is much the same as it is in nitromethane, but the ionization is much more exothermic. The dielectric constant of *m*-cresol, 12·4, is much less than that of nitromethane 37·4 (Maryott and Smith, U.S. Nat. Bur. Stand., Circular No. 514, 1951). Thus

if the solvent effect of *m*-cresol were determined by its dielectric constant according to the relation between free energy of ionization and dielectric constant obtained for the nitro-solvents (A. G. Evans, Price, and Thomas *loc. cit.*), we should expect the ionization of triphenylmethyl chloride in *m*-cresol to be so low that it could not be measured. We attribute the exceptional ionizing power of this solvent to the formation of hydrogen bonds between the hydroxyl group of the *m*-cresol and the Hal^- ion of the R^+Hal^- ion pair. Hydrogen bonding of the solvent with the Hal^- ion has been postulated earlier (*idem, loc. cit.*), to account for the fact that acetic acid is a better ionizing solvent than one would expect from its low dielectric constant. Hammett ("Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 54) has referred to this effect in considering the action of solvents on the ionization of triphenylmethyl chloride.

We also see in Table 2 that the change from chloride to bromide causes a four-fold increase in K_1, which corresponds to a decrease of 0·77 kcal. $mole^{-1}$ in ΔG°_{1a}. This increase in ionization from chloride to bromide is seen to be due to the more positive entropy of ionization of the bromide than of the chloride. We believe this to be due to the increase in size of the negative ion and the consequent reduction in the extent of "freezing" of solvent around this ion.

We have calculated the $\Delta G^\ddagger$ values for the S_N1 reactions of *tert.*-butyl chloride and bromide in 80% aqueous ethyl alcohol from the velocity constants obtained by Hughes (*J.*, 1935, 225) and Cooper and Hughes (*J.*, 1937, 1183) at 25°. These show a decrease of 2·1 kcal. $mole^{-1}$ from chloride to bromide, and this decrease runs parallel to the decrease of 0·77 kcal. $mole^{-1}$ which we obtain in ΔG°_{1a}.

Thus the change from chloride to bromide has an effect on the $\Delta G^\ddagger$ for S_N1 reactions which runs parallel to its effect on the ΔG°_{1a} value for reaction (1*a*) (cf. our previous papers).

The validity of our K values depends upon there being no appreciable concentration of uncoloured ions of the type (*A*) in which the R is covalently bonded to a solvent molecule (see Part II for a discussion of this point). If this ion were formed we should expect equilibria of the following type to exist:

$$R^+Hal^- + m\text{-}C_6H_4Me\cdot OH \rightleftharpoons \left[\begin{array}{c}Me\\ \\ O\\ H\end{array}\!\!\begin{array}{l}\\ \\ R\\ \\ \end{array}\right]^+ Hal^- \rightleftharpoons m\text{-}C_6H_4Me\cdot OR + HHal \quad . \quad (2)$$

(*A*)

since we know that the action of hydrochloric acid on a *m*-cresol solution of *m*-tolyl triphenylmethyl ether produces the characteristic R^+ spectrum. If such equilibria involved an appreciable concentration of positive ions such as (*A*) we should expect that the addition of excess of *m*-tolyl triphenylmethyl ether would have a marked effect on the equilibrium concentration of the carbonium ions. We find that the addition of this substance in a concentration one hundred times greater than that of the chloride has no effect on the optical density of a solution of triphenylmethyl chloride in *m*-cresol. We believe this to be strong evidence for our assumption that ions such as (*A*), if present, are in negligible concentration, and hence that the concentration of un-ionized halide is equal to the total concentration of halide minus the concentration of carbonium ions as measured by our absorption experiments.

We thank the Department of Scientific and Industrial Research for the award of a Maintenance Allowance (to A. P.), and the University College, Cardiff, for the award of a British Nylon Spinners Post-graduate Scholarship (to I. H. McE.).

CHEMISTRY DEPARTMENT, UNIVERSITY COLLEGE, CARDIFF. [*Received, April 27th*, 1955.]

The Production of Carbonium Ions by the Action of Metal Salts. Part II. The Extinction Coefficients of Carbonium Ions.*

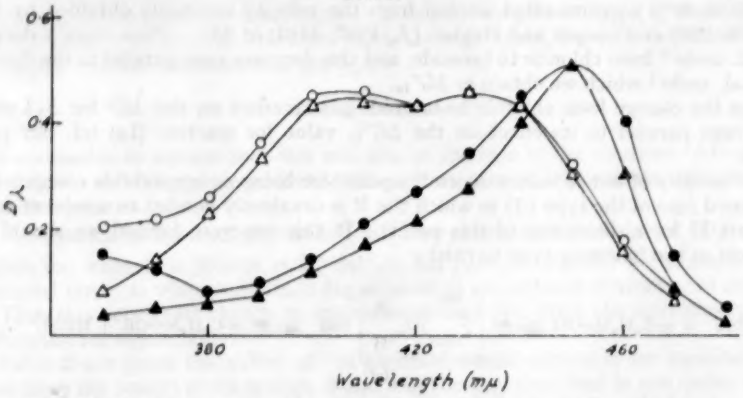
By J. W. Bayles, J. L. Cotter, and Alwyn G. Evans.

[Reprint Order No. 6367.]

The assumption that the extinction coefficient of triphenylmethyl ions in nitromethane solutions of mercuric chloride (whether as an ion pair $Ph_3C^+HgCl_3^-$ or as free ions $Ph_3C^+ + HgCl_3^-$) was the same as in concentrated sulphuric acid has been verified.

In previous papers (Bentley and A. G. Evans, *Research*, 1952, **5**, 535; Part I *), the interaction of mercuric chloride with triphenylmethyl chloride in nitromethane was investigated. The concentration of the carbonium ions present under these conditions was measured spectrophotometrically, with the assumption that the extinction coefficient of this ion in

Fig. 1.



○ *Mercuric bromide (total concn.* $1{\cdot}92 \times 10^{-3}$ *mole* $l.^{-1}$*) and triphenylmethyl bromide (total concn.* $1{\cdot}56 \times 10^{-6}$ *mole* $l.^{-1}$*) in nitromethane at* 16°.
△ *Triphenylmethyl alcohol (concn.* $1{\cdot}197 \times 10^{-5}$ *mole* $l.^{-1}$*) in* 98% *sulphuric acid.*
● *Mercuric bromide (total concn.* $1{\cdot}099 \times 10^{-3}$ *mole* $l.^{-1}$*) and tri-*p*-tolylmethyl bromide (total concn.* $7{\cdot}19 \times 10^{-6}$ *mole* $l.^{-1}$*) in nitromethane at* 16°.
▲ *Tri-*p*-tolylmethyl alcohol (concn.* $6{\cdot}538 \times 10^{-6}$ *mole* $l.^{-1}$*) in* 98% *sulphuric acid.*

these solutions was the same as in concentrated sulphuric acid. We justified this assumption on the grounds that the spectra of the ion in these solutions were almost identical. The assumption has now been tested as follows.

The addition of mercuric chloride to a nitromethane solution of triphenylmethyl chloride very markedly increases the ionization of the organic chloride. As shown in Part I, this involves the formation of ion pairs $Ph_3C^+HgCl_3^-$ and of free ions $Ph_3C^+ + HgCl_3^-$. If, in a given case, mercuric halide could be added to a triarylmethyl halide until no further increase in ionization occurred, we should know that complete ionization had been reached, and the calculated carbonium ion concentration for this solution should then indicate 100% ionization. These conditions are fulfilled for the addition of mercuric bromide to nitromethane solutions of triphenylmethyl or tri-*p*-tolylmethyl bromide. (The bromides, being more easily ionized than the chlorides, give complete ionization more easily.) For these solutions we find that when no further increase

* Part I, Bayles, A. G. Evans, and Jones, *J.*, 1955, 206.

in ionization occurs with increase in mercuric bromide concentration, our method of calculating the carbonium ion concentration gives 100% ionization, within the experimental accuracy.

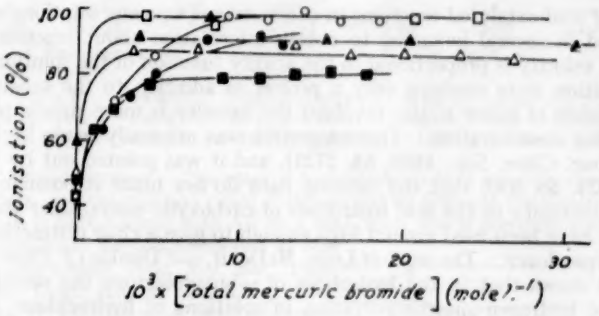
Experimental

Materials and Purification.—Nitromethane was obtained and purified as described by A. G. Evans, Jones, and Osborne (*Trans. Faraday Soc.*, 1954, **50**, 16). Triphenylmethyl bromide and tri-*p*-tolylmethyl bromide were prepared from the corresponding alcohols as described by A. G. Evans, McEwan, Price, and Thomas (preceding paper).

Mercuric bromide was an " AnalaR " product, sublimed before use.

Experimental Procedure.—This was the same as previously described (for references see *idem, loc. cit.*).

Fig. 2.



Tri-p-tolylmethyl bromide concn. : ○ 6·88, ● 7·19, △ 13·74, □ 13·76, ▲ 20·60 × 10^{-6} *mole* $l.^{-1}$.

Triphenylmethyl bromide concn. : 29·96 × 10^{-6} *mole* $l.^{-1}$.

Results.—Fig. 1 shows the spectra of the nitromethane solutions containing triarylmethyl bromide and mercuric bromide together with those of the corresponding alcohols in 98% sulphuric acid. The very close similarity for the two solvents establishes that the triarylmethyl ion is present in these nitromethane solutions. The percentage ionization has been calculated on the assumption that $\int D_\lambda d\lambda$ is the same for the two solutions containing the same concentration of triarylmethyl ions. [The alternative method of calculating the ionic concentration, by assuming $(D_\lambda)_{max.}$ to be the same for the same ionic concentration, leads to values which are identical, within experimental error, with the values used.] In Fig. 2 the percentage ionization, thus determined, is plotted against the total mercuric bromide concentration : when there is no further change of ionization the calculated percentage is between 80 and 100. This establishes that our method of calculating the carbonium ion concentration is correct within 20% and, therefore, that the values of $\Delta G°_{1a}$ and $\Delta G°_{2a}$ given in Part I are correct to within the experimental accuracy quoted there.

We thank the Department of Scientific and Industrial Research for a Maintenance Allowance to one of us (J. L. C.), and the Chemical Society for a Grant from the Research Fund towards the cost of chemicals.

Chemistry Department, University College, Cardiff. [*Received, April 27th*, 1955.]

The Kinetics of Ester Hydrolysis in Concentrated Aqueous Acids.

By R. P. Bell, A. L. Dowding, and J. A. Noble.

[Reprint Order No. 6331.]

Measurements are reported on the kinetics of hydrolysis of ethyl acetate and methyl formate in solutions of hydrochloric and sulphuric acid up to 10M, and on the acidity function of concentrated hydrochloric acid solutions. The results show that the reaction velocity is not proportional to the acidity function of the solution, being more closely proportional to the acid concentration. It is concluded that hydrolysis takes place by a bimolecular mechanism involving attack by a water molecule, in agreement with other evidence.

The kinetics of acid-catalysed reactions in concentrated aqueous solutions of strong acids have been used in several instances to obtain information about reaction mechanisms. If the reaction velocity is proportional to the acidity function of the solution it is believed that the transition state contains only a proton in addition to the substrate molecule, while if a molecule of water is also involved the velocity is more nearly proportional to the hydrogen-ion concentration. This suggestion was originally made by Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1932, **54**, 2721), and it was pointed out by Hammett and Paul (*ibid.*, 1934, **56**, 830) that the existing data do not make it possible to apply this criterion with certainty to the acid hydrolysis of carboxylic esters, since the acid concentrations which have been used are not high enough to give a clear distinction between the two types of dependence. The work of Long, McDevit, and Dunkle (*J. Phys. Colloid Chem.*, 1951, **55**, 829) shows that in the hydrolysis of γ-butyrolactone the reaction velocity is proportional to hydrogen-ion concentration in solutions of hydrochloric and perchloric acid up to about 4M. Since the γ-lactones are unstrained internal esters, it is likely that the same is true for simple carboxylic esters. This conclusion is in agreement with the mechanism usually accepted on other grounds, but it would be desirable to have direct evidence. It is difficult to extend the usual titrimetric method to high acid concentrations, since the reactions become inconveniently fast, and the titrations are inaccurate in the presence of a large excess of acid. The present paper describes kinetic measurements on the hydrolysis of ethyl acetate and methyl formate in solutions of strong acids up to 10M, physical methods being used to follow the fast reactions involved. The acidity functions of aqueous 6—10M-hydrochloric acid have also been measured.

Experimental

Hydrolysis of Ethyl Acetate.—This reaction was followed dilatometrically, it having been shown by Galeotti (*Z. physikal. Chem.*, 1911, **76**, 117) that the hydrolysis of a 10% aqueous solution is accompanied by a contraction of about 0·05%. The slower reactions were carried out in a dilatometer of conventional design with a volume of 50 c.c. and a capillary cross-section 0·08 mm.^{2}, thus giving a movement of the meniscus of about 150 mm. for the hydrolysis of a 4% solution of the ester. The course of these reactions was strictly of first order, and velocity constants were obtained either by observing the end-point, or by applying Guggenheim's method (*Phil. Mag.*, 1926, **7**, 538). However, for acid concentrations greater than about 2M the logarithmic plots were no longer strictly linear, especially near the beginning of the reaction. This was traced to the incomplete dissipation of heat evolved in the reaction, and experiments on the thermal characteristics of different types of glass tube showed that the error could be rendered negligible by using thin-walled tube of small diameter. The faster experiments were carried out in a dilatometer having a bulb consisting of a 30-cm. length of thin-walled tubing 1 cm. in diameter, and a capillary of cross-section 0·03 mm.^{2}. This revealed no departures from first-order behaviour for reactions with half-times down to 5 min. All kinetic experiments were carried out at 25°, and blank experiments showed that the temperature of the dilatometers fluctuated by less than 0·003°. Both dilatometers had a single tap.

The ester used was an " AnalaR " preparation redistilled before use. The acids used were

"AnalaR" reagents, and their concentration was related by titration to constant-boiling hydrochloric acid. The acid solution and the ester were both brought to thermostat temperature and degassed for a few minutes before mixing: this caused slight concentration changes (about 1%) in some of the acid solutions, detected by titrating a sample after degassing. Reliable dilatometer readings could be made about 5 min. after mixing. The results of these experiments are given in Table 1.

TABLE 1. *Hydrolysis of ethyl acetate at 25°.*

k = first-order velocity constant in sec.$^{-1}$. Acid concentrations in moles/l. of solution. Ester concentrations 4% unlesss otherwise stated.

Hydrochloric acid.

[HCl]	0·457	0·486	0·722	1·34	1·47	1·59	2·11	3·09
10^5k	5·19 *	5·38	8·10	17·8 †	18·0	20·8	27·4	45·0
H_0	+0·33	+0·29	+0·10	−0·24	−0·35	−0·40	−0·59	−0·94

[HCl]	4·75	5·48	6·51	7·91	8·11	9·06	10·10	10·20
10^5k	81·8	104	143	202	192	217	244	247
H_0	−1·55	−1·77	−2·20	−2·81	−2·89	−3·23	−3·57	−3·60

* Ester concn. 2%. † Ester concn. 8%.

Sulphuric acid.

$[H_2SO_4]$ ...	1·35	1·37	1·87	2·85	3·08	3·63	4·25	4·76	6·75
10^5k	18·8	19·8	30·9	56·1	65·5	79·7	104	128	192
H_0	−0·31	−0·33	−0·62	−1·15	−1·25	−1·50	−1·80	−2·05	−3·03

Hydrolysis of Methyl Formate.—This ester is hydrolysed in acid solution about 40 times as fast as ethyl acetate, and the reaction could therefore not be followed dilatometrically. However, the hydrolysis is endothermic, with $\Delta H \simeq 4$ kcal./mole, and is therefore suitable for study by the thermal-maximum method developed in this laboratory (Bell and Clunie, *Proc. Roy. Soc.*, 1952, *A*, **212**, 16; Bell, Gold, Hilton, and Rand, *Disc. Faraday Soc.*, 1954, **17**, 151), the more usual maximum being replaced here by a temperature minimum. The reaction was carried out by breaking bulbs containing about 2 g. of 17% ester solution into 50 c.c. of hydrochloric acid in a platinum vessel, the sensitivity of the single-junction thermocouple plus amplifier being 3000—4000 mm./degree. When aqueous solutions of methyl formate are mixed with concentrated hydrochloric acid there is a considerable instantaneous heat evolution. In the kinetic experiments this was eliminated by dissolving the ester in sodium nitrate solution instead of in water, heat being absorbed by the dilution of the sodium nitrate solution. For a given acid concentration the correct amount of sodium nitrate was determined by a series of experiments in which varying (insufficient) amounts of sodium nitrate were added to fixed quantities of ester and water in the bulb, and the instantaneous galvanometer deflection observed in each case. The correct amount of sodium nitrate was then estimated by extrapolating to zero galvanometer deflection. Typical plots of this kind are shown in Fig. 1. The temperature change caused by the reaction under adiabatic conditions (T_0; cf. Bell and Clunie, *loc. cit.*) was determined by experiments in a small double-walled glass vessel, in which the slow transfer of heat from the surroundings could be easily allowed for. The temperature was measured by the same amplifier and galvanometer as in the kinetic experiments, and the thermal characteristics of the two systems were directly compared by carrying out the neutralisation of sodium hydroxide by hydrochloric acid in each system. The results obtained for the rates of hydrolysis are given in Table 2, the velocity constants being derived from the observed value of T_m/T_0, and the measured cooling constant k_2 by the expression given by Bell and Clunie (*loc. cit.*) for first-order reactions.

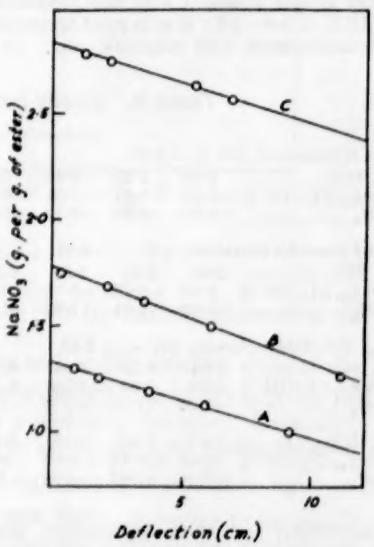


FIG. 1.

A, 2·67N-HCl. *B*, 3·58N-HCl. *C*, 5·79N-HCl.

TABLE 2. *Hydrolysis of methyl formate at 25°.*

Acid concentrations in moles/litre of solution. $k_2 = 0{\cdot}079_5$ sec.$^{-1}$. k_1 = first-order velocity constant in sec.$^{-1}$. Each T_m value is the mean of at least four experiments.

[HCl]	T_m/T_0	10^4k_1	H_0	$\log_{10}\{k_1/[HCl]\}$	$\log_{10}k_1 + H_0$
2·67	0·100	106	−0·79	−2·40	−2·76
3·58	0·130	153	−1·11	−2·37	−2·93
4·48	0·170	223	−1·40	−2·30	−3·05
5·30	0·205	291	−1·72	−2·26	−3·26
6·41	0·270	450	−2·11	−2·16	−3·46

Acidity Functions of Hydrochloric Acid.—The measurements already reported (Hammett and Deyrup, *loc. cit.*) extend only up to a concentration of 6M-hydrochloric acid, and were made with a visual colorimeter. We have therefore made further measurements in the range 2—10M using a Hilger Spekker absorptiometer. The three indicators used were *o*-nitroaniline (m. p. 71·7°), 4-chloro-2-nitroaniline (m. p. 116·0°), and *p*-nitrodiphenylamine (m. p. 133·0°), each after recrystallization from alcohol. The appropriate line of the mercury-discharge lamp was isolated by means of filters, and measurements were made at room temperature. The first two indicators showed a slight absorption at 4047 Å even in 95% sulphuric acid. Since this absorption was unchanged by recrystallisation it must be attributed to the protonated form of the indicator, and a small correction was applied to the optical densities of the more acid solutions, in which higher indicator concentrations had to be used in order to obtain an adequate absorption.

The results obtained are given in Table 3. The pK values of the first two indicators are those derived by Hammett from measurements in hydrochloric acid. The value of −2·35 given for *p*-nitrodiphenylamine was obtained from our own measurements by comparing the results obtained with this indicator with those for 4-chloro-2-nitroaniline in the range [HCl] = 5·0—5·5: it is in good agreement with the value obtained by Hammett (−2·38) from measurements with sulphuric acid. In the range [HCl] = 2—6 our values of H_0 are in fair

TABLE 3. *Acidity functions for aqueous hydrochloric acid.*

(Concentrations in moles/l. of solution.)

o-Nitroaniline, pK = − 0·17.

[HCl]	2·24	2·25	2·52	2·57	2·88	3·63
$\log_{10}\{[I]/[IH^+]\}$	−0·46	−0·45	−0·55	−0·57	−0·70	−0·97
H_0	−0·63	−0·62	−0·72	−0·74	−0·87	−1·14

4-Chloro-2-nitroaniline, pK = − 0·91.

[HCl]	2·68	3·30	5·00	5·39	5·49
$\log_{10}\{[I]/[IH^+]\}$	0·08	−0·13	−0·76	−0·84	−0·86
H_0	−0·83	−1·04	−1·67	−1·75	−1·77

p-*Nitrodiphenylamine*, pK = − 2·35.

[HCl]	5·04	5·35	5·40	5·67	6·78	6·80	7·30	7·33	7·43	7·56	7·79
$\log_{10}\{[I]/[IH^+]\}$	0·69	0·60	0·58	0·47	0·00	0·03	−0·20	−0·25	−0·28	−0·31	−0·45
H_0	−1·66	−1·75	−1·77	−1·88	−2·35	−2·32	−2·55	−2·60	−2·63	−2·66	−2·80

[HCl]	7·87	7·91	8·16	8·46	8·71	8·82	9·01	9·40	9·61	9·90
$\log_{10}\{[I]/[IH^+]\}$	−0·45	−0·48	−0·63	−0·64	−0·75	−0·85	−0·89	−1·01	−1·09	−1·17
H_0	−2·80	−2·83	−2·98	−2·99	−3·10	−3·20	−3·34	−3·36	−3·44	−3·52

agreement with those of Hammett, allowing for the different concentration scales used. The values of H_0 for hydrochloric acid given in Tables 1 and 2 were obtained by interpolation from a plot of both sets of data against concentration. For sulphuric acid Hammett's data were used directly.

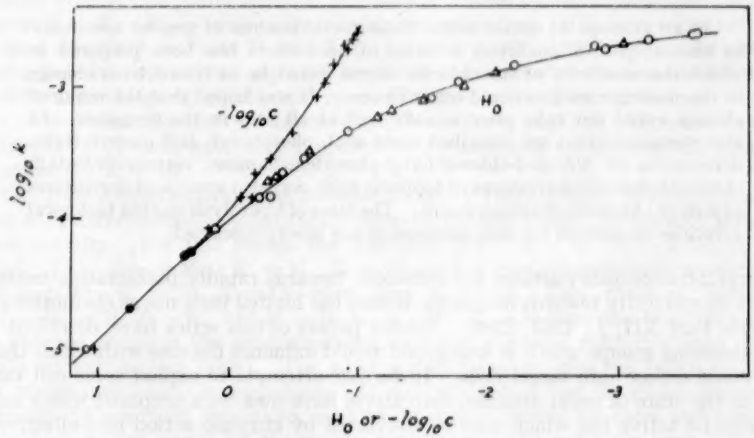
DISCUSSION.

Previous kinetic data on the acid hydrolysis of ethyl acetate extend up to [HCl] = 1·4 (Harned and Pfanstiel, *J. Amer. Chem. Soc.*, 1922, **44**, 2199), and our results over the same range are in good agreement with these. Fig. 2 shows plots of $\log_{10} k$ against H_0 and against $-\log_{10}$ [HCl] over the whole concentration range. The points for the two most

dilute solutions are taken from the results of Harned and Pfanstiel (*loc. cit.*). In the plot involving H_0 the data for both hydrochloric and sulphuric acids fall on the same curve, but this is far from linear, and its slope varies from close to unity in the more dilute solutions to about 0·1 at the highest concentrations. The plot against $-\log_{10}$ [HCl] is more closely linear, but bends noticeably upwards, its slope varying from unity to about 1·6 with increasing concentration. The results with sulphuric acid when plotted against $\log_{10}$ [H_2SO_4] (not shown in Fig. 2) lie slightly above the corresponding curve for hydrochloric acid: this is reasonable, since at the concentrations involved the first dissociation of sulphuric acid is complete, and the second present only to a small extent.

The data for the hydrolysis of methyl formate show a closely similar behaviour, as may be seen from the last two columns in Table 2. Neither is strictly constant, but there is a closer proportionality to concentration than to acidity function. In these experiments the acidity functions will be modified slightly by the presence of sodium nitrate (up to

FIG. 2.



○ *and* +, HCl; △, H_2SO_4.

0·15M), but Paul's results (*ibid.*, 1954, **76**, 3236) show that the salt effects involved will not be sufficient to alter our general conclusions.

The lack of parallelism between reaction velocity and acidity function excludes the unimolecular mechanism, in which the slow step is $R'\cdot CO\cdot\overset{+}{O}HR \longrightarrow R'\cdot\overset{+}{C}O + HOR$, the transition state being formed by simple addition of a proton to the ester. Since acyl–oxygen fission is well established for simple carboxylic esters, the only reasonable alternative is the bimolecular mechanism, involving the slow step $R'\cdot CO\cdot\overset{+}{O}HR + H_2O \longrightarrow R'\cdot CO\cdot\overset{+}{O}H_2 + HOR$ (cf. Datta, Day, and Ingold, *J.*, 1939, 838). According to the usually accepted view this should lead to a proportionality between reaction velocity and acid concentration, since the transition state contains a water molecule as well as a proton. This proportionality is only approximately found in our measurements. However, there are actually no compelling grounds for expecting an exact proportionality to acid concentration over an extended range. The data for the enolization of acetophenone (Zucker and Hammett, *ibid.*, 1939, **61**, 2791) and for the hydrolysis of γ-butyrolactone (Long, McDevit, and Dunkle, *loc. cit.*) extend only up to 4M-acid, and the theoretical interpretation given by Hammett depends upon the plausible but uncertain assumption that the ratio of activity coefficients $f_S f_{H_2O^+}/f_{S\text{-}H_2O^+}$ (where S is the substrate) is unity. Further, in the concentrated acid solutions which we have used the choice of concentration scale makes

a considerable difference : for example, there is a closer (though still not exact) proportionality between reaction velocity and acid concentration if the latter is expressed in moles per kg. of solvent rather than in moles per litre of solution. We conclude, therefore, that the most important criterion in this type of investigation is the presence or absence of parallelism between reaction velocity and acidity function, and that the exact dependence on acid concentration is a matter for further investigation.

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Aryl-2-halogenoalkylamines. Part XIV. Some Compounds possessing Latent Cytotoxic Activity.*

By W. C. J. ROSS, G. P. WARWICK, and, in part, J. J. ROBERTS.

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In an attempt to obtain aryldi-2-chloroethylamines of greater specificity as tumour-growth inhibitors a series of derivatives has been prepared in which the reactivity of the chlorine atoms would be increased by a change in the molecule such as could occur *in vivo*. It was hoped that the required change would not take place equally well at all sites in the organism. In this communication are described some acyl, phosphoryl, and phenylureido-derivatives of *NN*-di-2-chloroethyl-*p*-phenylenediamine, certain *NN*-di-2-chloroethylamino-derivatives of hippuric acid, and also some acyl derivatives of *p*-di-(2-chloroethyl)aminophenol. The rates of hydrolysis and the biological activities of some of the new compounds are briefly discussed.

MANY aryl-2-halogenoalkylamines are cytotoxic towards rapidly proliferating tissues but their lack of specificity towards neoplastic tissues has limited their use as chemotherapeutic agents (see Part XII, *J.*, 1953, 2386). Earlier papers of this series have described derivatives possessing groups which it was hoped would influence the ease with which the compound would diffuse into target cells. In further attempts to exploit some cell variable, as well as the state of rapid division, derivatives have now been prepared which may not themselves be active but which may be converted by enzymic action into effective compounds. As there is, as yet, no clear indication of an enzyme system which predominates in neoplastic tissue the first studies are necessarily empirical. In the present communication are described compounds which could be activated, in the sense that their chlorine atoms could become more reactive, by processes known to occur *in vivo*.

The *p*-amino-derivative of *NN*-di-2-chloroethylaniline (I; R = H) is known to be very effective (Part II, *J.*, 1949, 1972) and it has been shown (Haddow, *Ann. Rep. British Empire Cancer Campaign*, 1952, **30**, 28) that certain acylated derivatives also exhibit activity as inhibitors of the transplanted Walker rat carcinoma although the chemical reactivity of the chlorine atoms in these derivatives is lower than in the parent amine. For example, the acetyl (I; R = Ac) and the propionyl (I; R = Et·CO) derivative are effective; the benzoyl derivative (I; R = Bz) is, however, inactive. These results suggested that hydrolysis to the amine was responsible for activity, the more resistant benzoate being unaffected.

A number of new acylated derivatives of the amine (I) has now been prepared. Particular attention has been directed to including substituents in the acyl group which would result in lowered reactivity in the chloroethyl group. The incorporation of such groups leads to a greater activation on subsequent hydrolysis of the amide linkage. The compounds obtained include the mono-, di-, and tri-chloroacetyl, the iodoacetyl, the phenylacetyl, and the *p*-nitrobenzoyl derivatives. Some of the compounds prepared, together with their rates of hydrolysis under standard conditions and their biological activities (where available), are given in the Table. Especially interesting is the trifluoroacetyl

* Part XIII, *J.*, 1955, 890.

derivative* (I; R = CF_3·CO) which is hydrolysed only to the extent of 7%, compared with 42% for the acetate.

4-(Di-2-chloroethylamino)-2-methylaniline and the 2-methoxy-analogue have also been prepared mainly because they would have been reductive fission products of various azo-derivatives (see below); but the acetyl and the benzoyl derivative of the former were also prepared for biological test.

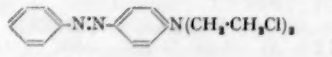
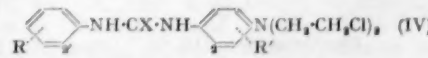
(I) *p*-NHR·C_6H_4·$N(CH_2·CH_2Cl)_2$ *p*-$(RO)_2PO·NH·C_6H_4·N(CH_2·CH_2Cl)_2$ (II)

In view of the reported higher activity of phosphoramidases in malignant tissue, compared with that on normal tissue [Ichihara, *J. Biochem.* (*Japan*), **1933**, **18**, 87; Gomori, *Proc. Soc. Exp. Biol. Med.*, **1948**, **69**, 407; see also Friedman and Seligman, *J. Amer. Chem. Soc.*, 1954, **76**, 655, 658] it appeared profitable to examine phosphoramidates related to the amine (I; R = H). Accordingly the diethyl (II; R = Et) and the diphenyl phosphoramidate (II; R = Ph) were prepared. Only the diethyl derivative was an active tumour-growth inhibitor.

Another type of compound which is probably activated by conversion into the amino-derivative (I; R = H) is di-2-chloroethylaminoazobenzene (III), some derivatives of which were described in Parts II and XII (*J.*, 1949, 1972; 1953, 2386). An extended series of azo-derivatives will be reported later. It is known that the azo-linkage may be replaced by a ureido-group in certain trypanocidal dyes without loss of biological activity (Burger, "Medicinal Chemistry," Interscience, New York, 1951, p. 842), so several urea derivatives (IV; X = O) have been prepared by the action of the appropriate *iso*cyanate on the amine (I; R = H).

In the *p*-(di-2-chloroethylamino)azobenzene series early results indicated that the insertion of electron-releasing substituents *ortho* to the azo-linkage favourably influenced cytotoxic activity. For this reason the 2-methyl- (IV; R = H, R′ = *o*-Me, X = O), 2′-methyl- (IV; R = *o*-Me, R′ = H, X = O), and 4′-methyl-diphenylurea derivative (IV; R = *p*-Me, R′ = H, X = O) were also prepared. Two thiourea derivatives (IV; R = R′ = H, X = S; and R = H, R′ = *o*-Me, X = S) have also been obtained.

The chlorine atoms in the azo-compounds have less chemical reactivity than those in the ureido-derivatives (see Table). The latter would, however, give rise to the even more reactive amino-compounds on hydrolysis. It was established that the ureido-linkage was stable under the standard conditions used to determine hydrolysis rates and hence the relatively high values found for the ureido-derivatives could not have been due to the partial formation of the very reactive *p*-phenylenediamine derivative (I; R = H). Prolonged heating of the *p*-tolylureido-derivative (IV; R = *p*-Me, R′ = H, X = O) in 50% aqueous acetone gave the corresponding di-2-hydroxyethylaminophenylureido-compound.

(III)  (IV) 

(IV*a*) Ph·N:CH·C_6H_4·$N(CH_2·CH_2Cl)_2$-*p* Ph·CH:CH·$C_6H_4(N·CH_2·CH_2Cl)_2$-*p* (IV*b*)

(IV*c*) *p*-$(Cl·CH_2·CH_2)_2N·C_6H_4·CH:N·C_6H_4·N(CH_2·CH_2Cl)_2$-*p*

The azomethine (IV*a*) was of considerable interest since it could be regarded as an isostere of two cytotoxic agents, namely, the azo-compound (III) and the stilbene derivative (IV*b*) (Ross, *J.*, 1949, 183), and for this reason the parent substance and its 4′-methoxy- and 3′-nitro-derivatives were prepared. In the organism the azomethine could yield the weakly growth-inhibitory *p*-(di-2-chloroethylamino)benzaldehyde by hydrolytic fission or *N*-4-(di-2-chloroethylamino)benzylaniline by enzymic reduction. The last compound, which would be expected to be active on account of the reactivity of its chlorine atoms, was prepared, for test, by catalytic hydrogenation of the azomethine (IV*a*). A tetra-2-chloroethylaminoazomethine (IV*c*) was obtained by condensing *p*-(di-2-chloroethylamino)-benzaldehyde with *p*-*NN*-di-2-chloroethyl-*p*-phenylenediamine. The closely related phenylhydrazone of *p*-(di-2-chloroethylamino)benzaldehyde was also prepared for test.

* The preparation of this compound was suggested in discussion with Dr. L. N. Owen.

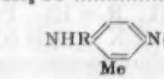
The hydrolysis rate of the azomethines could not be determined since decomposition into the constituent aldehyde and amine occurred under the standardised conditions for this test.

p-(Di-2-chloroethylamino)benzoic acid (V) is a moderately effective cytotoxic agent, for although the reactivity of the chlorine atoms in the free acid is low it is much higher in the ionised form which will predominate at physiological pH. In its esters activation of the chlorine atoms will be manifest only after hydrolysis of the ester linkage. The methyl ester has low biological activity whereas the ethyl ester is inactive; the methyl ester would be expected to be the more easily hydrolysed (cf. Hammett, " Physical Organic Chemistry," New York, 1940, p. 211).

Two other compounds of lowered chemical reactivity which could give rise to the aminobenzoic acid derivative (V) have now been prepared : *p*-(di-2-chloroethylamino)benzamide and ethyl *p*-di-(2-chloroethylamino)hippurate (VI) were obtained by the action of the acid

(V) *p*-$HO_2C{\cdot}C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ $HO_2C{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$-*p* (VI)

chloride on ammonia and glycine ester respectively. During this work the preparation of ethyl *p*-(di-2-chloroethylamino)benzoate was improved. The corresponding *m*-substituted amide and hippuric acid were similarly prepared. These amides and hippuric acid derivatives are not effective compounds and this suggests that the amide linkage is not readily hydrolysed *in vivo*.

Substituent R	Hydrolysis (%) *	Biological activity †
Diamine (I)		
Ac	42	+ve
Et·CO	40	+ve
Pr·CO	38	—
$CH_2F{\cdot}CO$	19	+ve
$CF_3{\cdot}CO$	7	—
$CH_2Cl{\cdot}CO$	23	—
$CHCl_2{\cdot}CO$	17	—
$CCl_3{\cdot}CO$	13	+ve
$CH_2I{\cdot}CO$	19	—
Bz	23	−ve
p-Me·$C_6H_4{\cdot}CO$	29	—
p-$O_2N{\cdot}C_6H_4{\cdot}CO$	18	—
Ph·$CH_2{\cdot}CO$	53	—
		
Ac	47	—
Bz	23	—
Phosphoramidates (II)		
Et	41	+ve
Ph	28	−ve
Azobenzene derivative (III)		
—	<1	+ve

Substituent R	Hydrolysis (%) *	Biological activity †
Urea (IV; R′ = H; X = O)		
H	34	+ve
H (R′ = 2-Me)	38	—
2′-Me	52	—
4′-Me	47	—
Thiourea (IV; R = H, X = S)		
H	14	—
H (R′ = 2-Me)	13	—
p-R·CO·$C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$		
Cl	—	−ve
NH_2	2	—
·$NH{\cdot}CH_2{\cdot}CO_2Et$	3	−ve
m-R·CO·$C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$		
Cl	—	−ve
NH_2	7	−ve
·$NH{\cdot}CH_2{\cdot}CO_2Et$	7	−ve
p-RO·$C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$		
H ‡	56	+ve
Ac ‡	15	+ve
Bz ‡	Bz ‡	+ve

* In 50% aqueous acetone at 66° during ½ hr. † As inhibitors of the growth of the transplanted Walker rat carcinoma. ‡ Measured by Dr. J. J. Roberts.

The chlorine atoms in the *O*-acetate and *O*-benzoate of *p*-(di-2-chloroethylamino)-phenol were shown to be less reactive than those in the free phenol (Table). In tumour-growth inhibition tests, however, the acetate and the benzoate are more effective than the phenol. This may be due to the liberation of the phenol within cells into which the free phenol could not so easily diffuse. An attempt to obtain *p*-(di-2-chloroethylamino)phenol by heating *NN*-di-2-chloroethyl-*p*-anisidine with hydriodic acid resulted in the formation of *N*-2-chloroethyl-*N*-2-iodoethyl-*p*-anisidine, previously obtained from *NN*-di-2-chloroethyl-*p*-anisidine and sodium iodide in aqueous acetone (Ross, *J.*, 1949, 2589). The required phenol was eventually obtained in low yield by the action of phosphorus

oxychloride on *p*-(di-2-hydroxyethylamino)phenol (I.G. Farbenind A.-G., Fr. P. **648,761**). Although the *p*-(di-2-chloroethylamino)phenyl benzoate was readily obtained by the action of benzoyl chloride in alkaline solution the acetate could not thus be conveniently prepared. Hydroxyethylation of *p*-aminophenyl acetate (Gatalis, *Ber.*, **1926**, **59**, 850), followed by treatment with phosphorus oxychloride, gave the required *p*-(di-2-chloroethylamino)-phenyl acetate.

Experimental

4-(*Di*-2-*chlorothylamino*)-2-*methyl*- *and* -2-*methoxy*-*aniline*.—*NN*-Di-2-chloroethyl-*m*-toluidine (Ross, *J.*, **1949**, **183**) was nitrosated by Everett and Ross's method (*J.*, **1949**, 1972), giving the 4-*nitroso*-derivative (NR_2 = 1), m. p. 103°, dark green needles from benzene–light petroleum (b. p. 60—80°) (Found: C, 50·8; H, 5·5; N, 11·0. $C_{11}H_{14}ON_2Cl_2$ requires C, 50·6; H, 5·4; N, 10·7%). Reduction of the nitroso-compound with stannous chloride as described in Part II, or more conveniently by hydrogenation over a palladium catalyst in methanol, gave the diamine which formed a *hydrochloride*, m. p. 200°, needles from ethanol–light petroleum (b. p. 60—80°) (Found: C, 46·8; H, 6·1; N, 9·9. $C_{11}H_{16}N_2Cl_2$,HCl requires C, 46·6; H, 6·0; N, 9·9%), and an *acetyl*, m. p. 125°, fine needles from benzene–light petroleum (b. p. 60—80°) (Found: C, 54·0; H, 6·4; N, 9·7. $C_{13}H_{18}ON_2Cl_2$ requires C, 54·0; H, 6·3; N, 9·7%), and a *benzoyl derivative*, m. p. 156—157°, short thick needles from ethanol (Found: C, 62·0; H, 6·0; N, 8·2. $C_{18}H_{20}ON_2Cl_2$ requires C, 61·5; H, 5·7; N, 8·0%).

NN-*Di*-2-*chloroethyl*-m-*anisidine* {obtained from *m*-anisidine as a colourless oil, n_D^{23} 1·5708, by the methods described in Part I: Found: Cl, 28·6, 28·4. $C_{11}H_{15}ONCl_2$ requires Cl, 28·6% [*styphnate*, prisms, m. p. 124—125° (decomp.) (from methanol) (Found: C, 41·3; H, 3·9; N, 11·1. $C_{17}H_{18}O_9N_4Cl_2$ requires C, 41·4; H, 3·7; N, 11·3%)]} was similarly converted into the 4-*nitroso*-derivative, m. p. 122°, stout dark green needles from benzene–light petroleum (b. p. 60—80°) (Found: C, 47·8; H, 5·2; N, 10·5. $C_{11}H_{14}O_2N_2Cl_2$ requires C, 47·7; H, 5·1; N, 10·1%), and into the 4-amino-derivative which gave a *monohydrochloride*, m. p. 194° (decomp.), short needles from ethanol–light petroleum (b. p. 60—80°) (Found: C, 43·6; H, 5·8; N, 9·6. $C_{11}H_{16}ON_2Cl_2$,HCl requires C, 44·1; H, 5·7; N, 9·4%).

Acyl Derivatives of NN-*Di*-2-*chloroethyl*-p-*phenylenediamine*.—These derivatives were prepared by the following general method. *NN*-Di-2-chloroethyl-*p*-phenylenediamine hydrochloride (Everett and Ross, *loc. cit.*) (1 mol.) was suspended in ether and shaken with 2N-sodium hydroxide (2·5 equiv.). When all the solid had dissolved the mixture was cooled in ice, and the acid chloride or anhydride was added with vigorous shaking. After 10 min. the ether layer was washed with water and dried (Na_2SO_4). In some instances it was necessary to submit the product to chromatography (benzene and activated alumina). The acyl derivatives were crystallised from benzene–light petroleum (b. p. 60—80°) unless otherwise stated. The following derivatives of *NN*-di-2-chloroethyl-*p*-phenylenediamine were obtained: N′-*butyryl*, plates, m. p. 103° (Found: C, 55·4; H, 6·7; N, 9·1. $C_{14}H_{20}ON_2Cl_2$ requires C, 55·5; H, 6·7; N, 9·2%); N′-*fluoroacetyl*, plates, m. p. 123—124° (Found: C, 49·4; H, 5·3; N, 9·7. $C_{12}H_{15}ON_2Cl_2F$ requires C, 49·2; H, 5·2; N, 9·6%); N′-*trifluoroacetyl*, prismatic needles, m. p. 109—110°, from light petroleum (b. p. 60—80°) (Found: C, 43·9; H, 4·2; N, 8·9. $C_{12}H_{13}ON_2Cl_2F_3$ requires C, 43·8; H, 4·0; N, 8·6%); N′-*chloroacetyl*, needles, m. p. 137—138° (Found: C, 46·7; H, 5·0; N, 9·3. $C_{12}H_{15}ON_2Cl_3$ requires C, 46·5; H, 4·9; N, 9·1%); N′-*dichloroacetyl*, needles, m. p. 135° (Found: C, 42·3; H, 4·3; N, 8·2. $C_{12}H_{14}ON_2Cl_4$ requires C, 41·9; H, 4·1; N, 8·1%); N′-*trichloroacetyl*, plates, m. p. 113—114·5° (Found: C, 38·9; H, 3·7; N, 7·6; Cl, 46·0. $C_{12}H_{13}ON_2Cl_5$ requires C, 38·1; H, 3·5; N, 7·4; Cl, 46·8%); N′-*iodoacetyl*, pale yellow needles, m. p. 149—150° (Found: C, 35·8; H, 4·0; N, 7·0. $C_{12}H_{15}ON_2Cl_2I$ requires C, 35·9; H, 3·8; N, 7·0%); N′-*phenylacetyl*, needles, m. p. 132·5° (Found: C, 61·4; H, 4·7; N, 8·7. $C_{18}H_{20}ON_2Cl_2$ requires C, 61·5; H, 5·7; N, 8·0%); N′-p-*nitrobenzoyl*, copper-coloured plates, m. p. 176°, from ethanol–benzene (Found: C, 53·1; H, 4·6; N, 11·7. $C_{18}H_{17}O_3N_3Cl_2$ requires C, 53·2; H, 4·5; N, 11·0%).

Phosphoramidates from NN-*Di*-2-*chloroethyl*-p-*phenylenediamine*.—*NN*-Di-2-chloroethyl-*p*-phenylenediamine hydrochloride (0·5 g.) was shaken with an excess of 2N-sodium carbonate, and the free base was extracted with ether. Triethylamine (1 ml.) was added to the dried ether solution, followed by diphenyl phosphorochloridate (0·5 ml.). After 10 min. at room temperature the solution was washed with water, dried, and evaporated. A benzene solution of the residue was passed through a column of activated alumina; further washing with benzene

slowly eluted the *diphenyl phosphoramidate* (0·55 g.) which formed prismatic needles, m. p. 128—130°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 56·7; H, 5·6; N, 5·9. $C_{23}H_{23}O_3N_2Cl_2P$ requires C, 56·8; H, 5·0; N, 6·0%). The *diethyl phosphoramidate*, m. p. 113—114°, forming prismatic needles from light petroleum (b. p. 60—80°), was similarly prepared (Found : C, 46·1; H, 6·5; N, 7·7. $C_{14}H_{22}O_3N_2Cl_2P$ requires C, 45·5; H, 6·3; N, 7·6%).

4-Di-2′-chloroethylaminodiphenylurea.—A suspension of *NN*-di-2-chloroethyl-*p*-phenylenediamine hydrochloride (2·69 g.) in ether (100 ml.) was shaken with 2N-sodium carbonate (20 ml.). To the dried ethereal layer was added phenyl *iso*cyanate (1·09 ml.) and when the mixture was heated the *diphenylurea* separated. It formed flattened needles, m. p. 150—152°, from benzene (Found : C, 58·2; H, 5·5; N, 11·9. $C_{17}H_{19}ON_3Cl_2$ requires C, 58·0; H, 5·5; N, 11·9%). *4-Di-2″-chloroethylamino-2-methyl-*, m. p. 170—171°, from ethyl acetate (Found : C, 58·3; H, 6·0; N, 11·3. $C_{18}H_{21}ON_3Cl_2$ requires C, 59·0; H, 5·8; N, 11·5%), *4-di-2″-chloroethylamino-2′-methyl-*, m. p. 159—161°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 59·4; H, 5·7; N, 11·2%), and *4-di-2″-chloroethylamino-4′-methyl-diphenylurea*, m. p. 162°, from benzene (Found : C, 59·5; H, 5·8; N, 11·2%), and *4-di-2″-chloroethylamino-*, m. p. 147°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 55·7; H, 5·3; N, 11·6. $C_{17}H_{19}N_3Cl_2S$ requires C, 55·4; H, 5·2; N, 11·4%), and *4-di-2″-chloroethylamino-2-methyl-diphenylthiourea*, m. p. 169°, from ethyl acetate (Found : C, 56·3; H, 5·7; N, 11·3. $C_{18}H_{21}N_3Cl_2S$ requires C, 56·6; H, 5·5; N, 11·0%) were similarly prepared (all needles) from the appropriate reactants.

Hydrolysis of 4-Di-2″-chloroethylamino-4′-methyldiphenylurea.—A preliminary experiment showed that *s*-diphenylurea was unchanged when heated in 50% aqueous acetone for 10 hr. When 4-di-2″-chloroethylamino-4′-methyldiphenylurea was heated under reflux in 50% aqueous acetone for 3 hr. the corresponding *(dihydroxyethyl)amino*-derivative, m. p. 168°, needles, from ethyl acetate, was formed (Found : C, 65·3; H, 7·3; N, 13·0. $C_{17}H_{21}O_3N_3$ requires C, 65·6; H, 7·0; N, 12·8%).

N-4-(Di-2′-chloroethylamino)benzylideneaniline.—A solution of *p*-(di-2-chloroethylamino)-benzaldehyde (2·46 g.) and aniline (1 ml.) in dry ether (100 ml.) was concentrated to 25 ml. and then heated under reflux for 1 hr. On evaporation the solution gave a yellow oil which slowly solidified. The *azomethine* (2·35 g.) formed plates, m. p. 62—64°, from ethanol–light petroleum (b. p. 60—80°) (Found : C, 63·6; H, 5·8; N, 8·9. $C_{17}H_{18}N_2Cl_2$ requires C, 63·6; H, 5·7; N, 8·7%). When the azomethine (1 g.), dissolved in ethanol (20 ml.), was hydrogenated at room temperature over Raney nickel the theoretical volume of gas was taken up during 2½ hr. On saturation of the filtered solution with hydrogen chloride and addition of ether the *hydrochloride* of *N-4-(di-2′-chloroethylamino)benzylaniline* (0·65 g.) separated as a pale cream-coloured powder, m. p. 145° (decomp.) (Found : equiv. by potentiometric titration, 199. $C_{17}H_{20}N_2Cl_2,2HCl$ requires equiv., 198). *N-4-(Di-2′-chloroethylamino)-benzylidene-p-anisidine*, plates, m. p. 93, from ethanol (Found : C, 61·3; H, 5·8; N, 8·1. $C_{17}H_{20}ON_2Cl_2$ requires C, 61·5; H, 5·7; N, 8·0%), *N-4′-(di-2-chloroethylamino)benzylidene-3-nitroaniline*, orange needles, m. p. 126—128·5°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 55·5; H, 4·8; N, 11·2. $C_{17}H_{17}O_2N_3Cl_2$ requires C, 55·7; H, 4·7; N, 11·5%), and *4 : 4′-bis(di-2-chloroethylamino)benzylideneaniline*, straw-coloured needles, m p. 134—135°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 55·0; H, 5·6; N, 9·0. $C_{21}H_{25}N_3Cl_4$ requires C, 54·7; H, 5·5; N, 9·1%), were prepared by similar condensation of the appropriate aldehyde and amine. The last compound rapidly darkened unless stored in the dark.

p-(Di-2-chloroethylamino)benzaldehyde Phenylhydrazone.—Heating the aldehyde (5 g.) and phenylhydrazine (2·2 g.) in ether (160 ml.) under reflux for 1 hr. gave the *phenylhydrazone* (5·9 g.), plates, m. p. 95—96° (from ethanol) (Found : C, 60·4; H, 5·8; N, 12·0. $C_{17}H_{19}N_3Cl_2$ requires C, 60·7; H, 5·7; N, 12·5%). This is converted into a dark resin in 2 weeks in a sealed container.

Ethyl p-*(Di-2-hydroxyethylamino)benzoate.*—(*a*) Ethylene oxide (25 ml.) in acetone (20 ml.) was added to a solution of ethyl *p*-aminobenzoate (20 g.) in water (40 ml.), acetone (40 ml.), and acetic acid (5 ml.). The mixture was heated at 50° and stirred for 8 hr.; then ethylene oxide (20 ml.) was added and stirring continued for a further 8 hr. The product was passed in benzene through activated alumina; the column was washed successively with benzene, benzene–ether (1 : 1), and ether. Early eluates contained *ethyl* p-*2-hydroxyethylaminobenzoate*, m. p. 61—61·5°, which formed flattened needles from benzene (Found : C, 63·0; H, 7·0; N, 6·7. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%). Later eluates contained the di-(hydroxyethyl)amino-ester, m. p. 92—93·5°, which formed plates from benzene (Found : C, 61·5; H, 7·5; N, 5·6. Calc. for $C_{13}H_{19}O_4N$: C, 61·6; H, 7·6; N, 5·5%). Everett and Ross (*loc. cit.*) gave m. p. 70° for the latter compound which they obtained as prisms from benzene.

All preparations now form the plates of higher m. p. and it appears that the product previously obtained was a different crystalline modification. In B.P. 128,912/1919 the di(hydroxyethyl)-amino-compound is described as having m. p. 94°.

(*b*) When ethyl *p*-aminobenzoate (16·5 g.), ethylene oxide (20 ml.), and 2N-acetic acid (20 ml.) were heated in a sealed tube at 130° for 5 hr. the di-2-hydroxyethylamino-ester, m. p. 90°, was the only product.

p-(*Di-2-chloroethylamino*)*benzoyl Chloride*.—Ethyl *p*-(di-2-hydroxyethylamino)benzoate (10 g.) was heated under reflux for 15 min. in benzene (100 ml.) containing thionyl chloride (10 ml.). Concentrated hydrochloric acid (70 ml.) was added to the cooled solution, and the mixture was distilled until all the benzene and 20 ml. of water had passed over. The remaining solution was then heated under reflux for a further 1½ hr. during which the *p*-(di-2-chloroethylamino)benzoic acid separated. It formed prisms, m. p. 168, from benzene–*cyclo*hexane (1 : 2) (yield 7·5 g.). The acid (2 g.) was heated for 15 min. with thionyl chloride (4 ml.) in benzene (40 ml.). The residue obtained after evaporation under reduced pressure crystallised from ether–light petroleum (b. p. 60—80°). p-(*Di-2-chloroethylamino*)*benzoyl chloride* formed plates, m. p. 83—84° (Found: C, 47·7; H, 4·5; N, 5·0. $C_{11}H_{12}ONCl_3$ requires C, 47·1; H, 4·3; N, 5·0%). The acid chloride was extremely sensitive to hydrolysis and was used immediately after purification. The *amide* was prepared by shaking an ethereal solution of the acid chloride with concentrated aqueous ammonia. It formed slender needles, m. p. 125—126°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 50·5; H, 5·5; N, 10·9. $C_{11}H_{14}ON_2Cl_2$ requires C, 50·6; H, 5·4; N, 10·7%).

Ethyl p-(*Di-2-chloroethylamino*)*hippurate*.—When the Schotten–Baumann method described below for the *m*-isomer was used, only *p*-(di-2-chloroethylamino)benzoic acid could be isolated. Because of the lability of the acid chloride the reaction with glycine had to be carried out in dry acetone. Glycine ester hydrochloride (10 g.) was mixed with an excess of powdered sodium hydroxide and moistened with water. The paste was extracted with acetone (50 ml.) and the extract was dried (K_2CO_3). Finely powdered acid chloride (2 g.) was then added to the filtered solution and this was left at room temperature for ½ hr., then diluted with water and extracted with ether. *Ethyl* p-(*di-2-chloroethylamino*)*hippurate* formed thin needles, m. p. 73·5—74°, from ether–pentane (Found: C, 52·2; H, 5·8; N, 7·8. $C_{15}H_{20}O_3N_2Cl_2$ requires C, 51·9; H, 6·0; N, 8·1%).

Ethyl m-(*Di-2-chloroethylamino*)*hippurate*.—*m*-(Di-2-chloroethylamino)benzoic acid (Everett, Roberts, and Ross, *J.*, 1953, 2386), its *acid chloride*, m. p. 79—81°, prisms from ether–light petroleum (b. p. 60—80°) (Found: C, 47·2; H, 4·3; N, 5·0. $C_{11}H_{12}ONCl_3$ requires C, 47·1; H, 4·3; N, 4·9%), and its *amide*, m. p. 110—112°, flattened needles from benzene–pentane (Found: C, 50·3; H, 5·6; N, 10·5. $C_{11}H_{14}ON_2Cl_2$ requires C, 50·6; H, 5·4; N, 10·7%), were similarly prepared. A solution of the acid chloride (1 g.) in ether (25 ml.) was shaken vigorously with a solution of glycine ester hydrochloride (0·625 g.) in N-sodium hydroxide (7 ml.). Sufficient N-sodium hydroxide (4 ml.) was then added to render the solution alkaline to phenolphthalein. The ether layer was then dried and evaporated, giving a yellow oil which was passed in benzene–light petroleum (b. p. 60—80°) (1 : 1) through activated alumina. After the early elution of amorphous material *ethyl* m-(*di-2-chloroethylamino*)*hippurate* (300 mg.) was obtained. It formed fine needles, m. p. 100°, from light petroleum (b. p. 60—80°) (Found: C, 51·9; H, 5·8; N, 7·9. $C_{15}H_{20}O_3N_2Cl_2$ requires C, 51·9; H, 6·0; N, 8·1%).

p-(*Di-2-chloroethylamino*)*phenol* (with J. J. Roberts).—*p*-(Di-2-hydroxyethylamino)phenol, prepared by the action of ethylene oxide on *p*-aminophenol in dilute acetic acid, formed prisms, m. p. 140°, from acetone (Found: C, 60·9; H, 7·8; N, 7·2. Calc. for $C_{10}H_{15}O_3N$: C, 60·9; H, 7·7; N, 7·1%). The *triacetate* formed prisms, m. p. 78°, from aqueous ethanol (Found: C, 59·1; H, 6·7. $C_{16}H_{21}O_6N$ requires C, 59·4; H, 6·5%), and the *tribenzoate* formed prisms, m. p. 84°, from ethanol (Found: C, 72·8; H, 5·4. $C_{31}H_{27}O_6N$ requires C, 73·1; H, 5·3%). The dihydroxyethylaminophenol (10 g.) and phosphorus oxychloride (10 ml.) were heated under reflux for 1 hr., after which the mixture was evaporated under reduced pressure and concentrated hydrochloric acid (20 ml.) was added. After 1 hour's heating the solution was diluted with water and extracted with chloroform. The dark extract was passed in benzene through activated alumina which was further washed with benzene. Finally elution with chloroform gave the chloroethylaminophenol as an oil which formed a *hydrochloride*, m. p. 168° (Found: C, 44·8; H, 5·5; N, 5·1. $C_{10}H_{13}ONCl_2,HCl$ requires C, 44·3; H, 5·2; N, 5·2%), and a *picrate*, m. p. 146°, small prisms from benzene (Found: C, 42·0; H, 3·8; N, 11·8. $C_{16}H_{16}O_8N_4Cl_2$ requires C, 41·5; H, 3·5; N, 12·1%). p-(*Di-2-chloroethylamino*)*phenyl benzoate*, prepared by shaking the free phenol (1 g.) in 10% aqueous sodium hydroxide with benzoyl chloride (1 g.)

for 15 min., formed prisms, m. p. 84—86°, from light petroleum (b. p. 60—80°) (Found: C, 60·1; H, 5·2; N, 4·1; Cl, 20·5. $C_{17}H_{17}O_3NCl_2$ requires C, 60·4; H, 5·1; N, 4·1; Cl, 20·9%).

p-(*Di-2-chloroethylamino*)*phenyl Acetate.*—*p*-Aminophenyl acetate was treated with ethylene oxide in 2N-acetic acid in the usual way, and the resultant NN-*di-2-hydroxyethyl* derivative formed plates, m. p. 82·5°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 60·2; H, 7·2. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2%). Heating the diol (10 g.) with phosphorus oxychloride (10 ml.) in benzene (30 ml.) for 45 min. gave p-(*di-2-chloroethylamino*)*phenyl acetate* (2 g.) as an oil (Found: Cl, 25·5. $C_{12}H_{15}O_2NCl_2$ requires Cl, 25·7%).

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The Stereochemistry of Triarylstibines. Synthesis and Optical Resolution of p-*Carboxyphenyl-2-diphenylylphenylstibine.*

By I. G. M. CAMPBELL.

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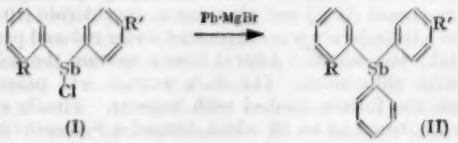
The synthesis of two stibines in which antimony is attached to three different aryl groups and the resolution of one of these, *p*-carboxyphenyl-2-diphenylylphenylstibine, into (+)- and (−)-forms, $[\alpha]_D^{20}$ ±47·0°, are described. The enantiomers are optically stable in toluene and in *p*-xylene at the boiling point. The optical stability of the stibine is contrasted with the lability of enantiomeric arylamines and possible reasons for the difference are discussed. The ultraviolet spectrum of 2-diphenylyl-*p*-tolylphenylstibine and of 9-*p*-tolyl-9-stibiafluorene are recorded and compared with that of triphenylstibine.

THE considerable optical stability observed in the stibiafluorenes, compounds in which antimony occurs as a tervalent heteroatom in a five-membered ring (*J.*, 1955, 1662), suggested that it might prove possible to demonstrate optical activity in stibines in which the antimony atom was not held in a ring, but attached to three different groups. Substituted triarylstibines were considered the most promising material for such an attempt, but apparently no compound of this type, *e.g.*, (II), in which antimony is attached to three different aryl groups has been prepared. The most obvious route is the reaction of a Grignard reagent on an unsymmetrical diarylstibinous halide (I), and some information on this type of compound was available, for several members of the series had been obtained by the reduction of the diarylstibinic chlorides used in the synthesis of stibiafluorenes. However, all these diarylstibinous halides contained a 2-diphenylyl group (I;



(I) (II)

R = Ph) and were therefore considered unsuitable for the purpose, because of the possibility of restricted rotation. To avoid such complication, the introduction of a 4-diphenylyl group was attempted, but the interaction of diphenyl-4-diazonium antimony chloride with

p-ethoxycarbonylphenylstibonous chloride failed to give the expected product. Instead, a very insoluble compound was obtained, along with a considerable yield of diphenyl and ethyl benzoate. Disproportionation had apparently occurred, for reduction of the insoluble compound with stannous chloride gave di-4-diphenylylstibinous chloride, m. p. 200°. Similar attempts to introduce *p*-bromo- or *p*-chloro-phenyl groups also failed, and, as unsymmetrical stibinous chlorides were available from previous work, it was decided to investigate the reaction of a Grignard reagent on these, despite the structural disadvantages of the 2-diphenylyl group.

The reaction of phenylmagnesium bromide on the chloride (I; R = Ph, R′ = Me) gave the expected triarylstibine in good yield, although initially it was necessary to isolate it by conversion into the dibromide and subsequent reduction. When a crystalline specimen had been obtained, this process became unnecessary, because seeding sufficed. The corresponding reaction with the ester (I; R = Ph, R′ = CO_2Et) presented more difficulty, as, apparently, the rates of the competitive reactions, replacement of halogen and attack on the ester group, did not differ widely. But conditions were found whereby the triaryl-

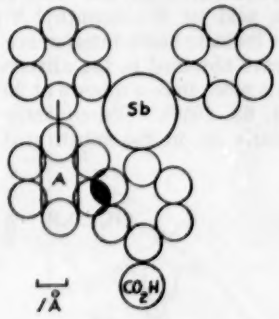


FIG. 1.
C–C bond, aromatic, 1·4 Å.
C–C bond, diphenyl, 1·48 Å.
C–CO_2H bond, 1·56 Å.
C–Sb bond, 2·11 Å.
Angle CSbC, 120°.

stibine (II; R = Ph, R′ = CO_2Et) could be obtained in 50—55% yield, and hydrolysis gave *p*-carboxyphenyl-2-diphenylylphenylstibine (II; R = Ph, R′ = CO_2H), m. p. 199—200°.

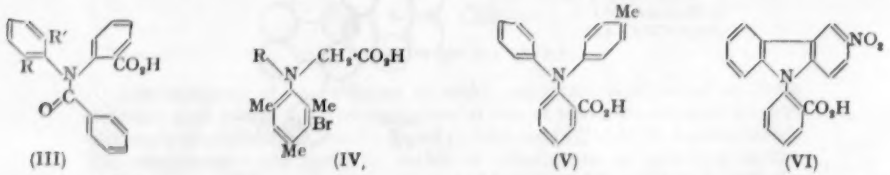
Resolution of the acid was readily accomplished by the use of (+)-1-phenylethylamine. Both diastereoisomers were obtained optically pure, but the yields were low, largely because the salts tended to separate as gels from concentrated solution. The active acids, $[\alpha]_D$ −46·9° and +47·2°, were optically stable at room temperature; the rotations of the pyridine solutions were unchanged when examined after three months. Further, the rotation of a toluene solution of the (−)-acid, $[\alpha]_D^{29}$ −57·4°, was unaffected by one hour's boiling and a solution in *p*-xylene, $[\alpha]_D^{18}$ −52·3°, showed the same value after two hours' boiling, so the compound possesses considerable optical stability. An attempt to racemise the (−)-acid in decalin (b. p. 188—189°) resulted in a fall in rotation from $[\alpha]_D^{23}$ −47·0° to −22·6° in 30 minutes, but oxidation rather than a true racemisation had occurred for the solid, m. p. 290—294°, which separated on cooling the solution was the stibine oxide. No evidence was obtained of the rapid catalytic racemisation observed so frequently with the active stibiafluorenes. The (−)-acid in chloroform was unaffected by dry hydrogen chloride, the most potent catalyst in the stibiafluorene series, until its concentration was sufficient to cause chemical decomposition.

As all attempts to isolate optically active isomers of simple tervalent nitrogen, phosphorus, and arsenic compounds have so far failed, the very considerable optical stability of this stibine suggests that the dissymmetry is caused by restricted rotation within the molecule rather than the stable pyramidal arrangement of the three Sb–C bonds. That restricted rotation of the simple diphenyl type cannot be responsible for the enantiomers is clear, because no group is present in the *meta*-position of the 2-diphenylyl group to give dissymmetry. But scale models and drawings (Fig. 1) indicate considerable hindrance to the free rotation of the groups attached to the antimony atom with a planar arrangement

of bonds at 120°, if the two benzene rings of the 2-diphenylyl group remain coplanar, and slight hindrance if these rings are at right angles to each other. On this planar model one can show that synchronised rotation of the groups is possible and can give the molecule symmetrical configuration at least momentarily. Fig. 1 is constructed by using covalent and not van der Waals radii (hydrogen atoms have been omitted for clarity) so that the overlap is underestimated, and A represents an alternative position but not necessarily the " thickness " of the second benzene ring of the diphenylyl group; but the Figure gives a crude picture of the restricted molecule when the antimony bonds are arranged at 120°.

The situation resembles that found in the *N*-benzoyldiphenylamine-2-carboxylic acids (III) studied by Jamison and Turner and their collaborators (*J.*, **1938**, **1646**; **1940**, **264**; **1955**, **145**), and also in the arylamines (IV) examined by Adams and his school (*J. Amer. Chem. Soc.*, **1954**, **76**, **5478**, and earlier papers listed therein). Unfortunately, in all the optically active compounds obtained, alkyl, acyl, or aroyl in addition to aryl groups are attached to the nitrogen atom so that no completely analogous compound is available for comparison. Meisenheimer and his collaborators investigated substituted triphenylamines (V) (*Ber.*, **1924**, **57**, **1744**) but failed to obtain evidence of resolution in *N*-phenyl-*N*-*p*-tolylanthranilic acid or *N*-α-naphthyl-*N*-phenylanthranilic acid, although models of these compounds indicate steric interference.

The enantiomers obtained in the nitrogen series are all optically labile with half-lives ranging from little more than a minute at 20° (*J.*, 1955, 145) to 28 hours at 118° (*J. Amer. Chem. Soc.*, **1941**, **63**, **2859**). Consequently the optical stability of the stibine is rather striking, particularly as, in the substituted *N*-benzoyldiphenylamine-2-carboxylic acids



the small diameter of nitrogen results in overcrowding comparable with that occurring in the stibine, as far as can be judged from models and projections. From a purely mechanical viewpoint, therefore, the most hindered nitrogen compounds would not be expected to attain the planar configuration necessary for racemisation at all readily. However, these comparisons are necessarily qualitative and the presence of the benzoyl group in Jamison and Turner's compounds may increase the ease of synchronised rotations of the groups as indicated by models with C–N–C bonds at either 109·5° or 120° (*J.*, **1955**, **147**). That this synchronised rotation may play a considerable part in racemisation might be inferred by comparison of Meisenheimer's failure to resolve the amine (V) with the successful resolution of 9-*o*-carboxyphenyl-3-nitrocarbazole (VI) (Patterson and Adams, *J. Amer. Chem. Soc.*, **1933**, **55**, **1069**) in which two of the rings which restrict the rotation of the *o*-carboxyphenyl group are held in a plane. It has been established by Jamison and Turner (*loc. cit.*) and Adams (*J. Amer. Chem. Soc.*, **1940**, **62**, **2191**) that the dissymmetry of the arylamines is caused by restricted rotation rather than a formally asymmetric tervalent nitrogen atom. But it is improbable that the bonds from nitrogen to the three substituent groups are planar, for triphenylamine has a dipole moment of 0·47 D (Cowley, *J.*, **1952**, **3557**) and the C–N–C angle has been calculated as 114° (Leonard and Sutton, *J. Amer. Chem. Soc.*, **1948**, **70**, **1564**), so that the restriction causing dissymmetry must occur in a rather flat pyramid. The dipole moment of triphenylstibine is 0·57 D (Bergmann and Schütz, *Z. physikal. Chem.*, **1932**, **19**, *B*, **401**) which leads to a value of 112—113° for the C–Sb–C angle by a simple calculation (the necessary data are not available for the more refined method of Leonard and Sutton), so that the situation is very similar. But the reason for the great difference in optical stability is not obvious, unless one postulates that restriction in the nitrogen series is eased by an inversion of the pyramidal molecule which does not occur readily in the stibine.

The explanation may lie in the difference in atomic structure of the central atom in the two series, for *d*-orbitals are available in antimony and not in nitrogen. The energy required to flatten NH_3 is smaller than that required to flatten PH_3, AsH_3, or SbH_3 (Mulliken, *J. Amer. Chem. Soc.*, 1955, **77**, 887), the stabilisation of the pyramidal form of the last three hydrides being favoured by $p\pi$–$d\pi$ hybridisation. If, in the optically active stibine, the *d*-orbitals of antimony participate in the Sb–C bonding, the increased difficulty of flattening the pyramidal molecule would provide some explanation of the optical stability of the compound.

It seemed of interest to examine the ultraviolet absorption spectrum of 2-diphenylylphenyl-*p*-tolylstibine for comparison with that of triphenylstibine in which the broad absorption band indicates conjugation between the benzene rings and the antimony atom (Campbell and Poller, *Chem. and Ind.*, 1953, 1126). The curves *A* and *B* in Fig. 2 show that the additional benzene ring causes little change in the position of absorption, but increases the intensity as would be expected. The characteristic shift of absorption to

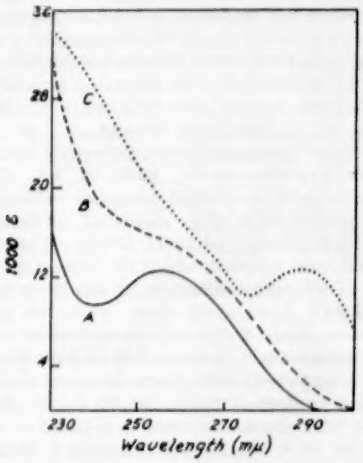


FIG. 2.

A, *Triphenylstibine.*
B, 2-*Diphenylylphenyl*-p-*tolylstibine.*
C, 9-p-*Tolyl*-9-*stibiafluorene.*

longer wavelength characteristic of the methyl group is absent, or masked by other effects, and the curve is greatly smoothed out. The spectrum of 9-*p*-tolyl-9-stibiafluorene (*J.*, 1950, 3109) is included to show the pronounced shift to longer wavelength which occurs on ring closure.

EXPERIMENTAL

Attempted Preparation of p-*Ethoxycarbonylphenyl*-4-*diphenylylstibinous Chloride.*—The diazonium antimony chloride double salt, obtained from 4-aminodiphenyl (8·5 g.) in the usual way, was decomposed in ethanol (50 ml.) containing *p*-ethoxycarbonylphenylstibonous chloride (17 g.) and copper powder (0·2 g.) at 50°. As the double salt decomposed, the mixture became dark brown and an insoluble deposit was formed. This solid (5 g.) could not be crystallised satisfactorily and was suspended in acetone (30 ml.) and reduced with stannous chloride (5 g.). Addition of 3·5N-hydrochloric acid (10 ml.) to the filtered solution precipitated a pale grey solid (3 g.) which, after crystallisation from carbon tetrachloride and from benzene, proved to be *di*-4-*diphenylylstibinous chloride*, m. p. 200° (Found: C, 61·9; H, 4·2. $C_{24}H_{18}ClSb$ requires C, 62·2; H, 3·9%). Acidification of the original dark brown filtrate precipitated diphenyl and ethyl benzoate, but no further organometallic compound was obtained.

2-*Diphenylylphenyl*-p-*tolylstibine.*—2-Diphenylyl-*p*-tolylstibinous chloride (8 g., 0·02 mole) (*J.*, 1950, 3112) in dry benzene (30 ml.) was added to the Grignard reagent prepared from bromobenzene (6·3 g., 0·04 mole) in ether, and the whole boiled for 15 min. After cooling, the mixture was extracted with saturated aqueous ammonium chloride and the benzene–ether layer separated, dried, and evaporated. A pale yellow syrup was obtained but did not crystallise,

consequently bromine in carbon tetrachloride was added to the syrup (0·5 g.) until a faint permanent colour remained, and the dibromide was precipitated by addition of light petroleum (b. p. 60—80°). Recrystallisation from light petroleum gave *2-diphenylylphenyl-p-tolylstibine dibromide*, m. p. 169—170° (0·4 g.) (Found: C, 49·7; H, 3·7. $C_{25}H_{21}Br_2Sb$ requires C, 49·8; H, 3·5%). Attempts to reduce this to the stibine by stannous chloride in ethanol containing aqueous hydrochloric acid failed, but produced the corresponding *dichloride*, m. p. 125—126° (Found: C, 57·8; H, 4·1. $C_{25}H_{21}Cl_2Sb$ requires C, 58·4; H, 4·1%). Reduction of this, or of the dibromide, in hot ethanol containing a few drops of ammonia with hydrogen sulphide gave *2-diphenylylphenyl-p-tolylstibine*, m. p. 81—83° after recrystallisation from ethanol–ethyl acetate, from which it separated as rosettes of small needles (Found: C, 67·2; H, 5·0. $C_{25}H_{21}Sb$ requires C, 67·7; H, 4·8%). When the main bulk of the syrup obtained in the Grignard reaction was seeded with this material, crystallisation occurred and the pure stibine (5 g.) was obtained.

2-Diphenylyl-p-ethoxycarbonylphenylphenylstibine.—Initial attempts to prepare this by the same procedure using one or two mols. of Grignard reagent failed but, by reversing the order of addition of the reactants so that the stibinous chloride was initially in excess, the required compound was obtained. The Grignard reagent prepared from bromobenzene (6·3 g., 0·04 mole) was added slowly to 2-diphenylyl-*p*-ethoxycarbonylphenylstibinous chloride (9·2 g., 0·02 mole: *J.*, 1952, 4450) in benzene (40 ml.) at 0°, and the mixture was boiled for 15 min., cooled, and decomposed with saturated aqueous ammonium chloride. The syrup obtained on evaporating the organic layer failed to crystallise, and a small quantity was converted into the *dibromide*, m. p. 148—150° (Found: C, 48·7; H, 3·5. $C_{27}H_{23}O_2Br_2Sb$ requires 49·1; H, 3·5%). Again attempted reduction with stannous chloride in ethanol gave the *dichloride*, m. p. 109—110° (Found: C, 56·5; H, 4·1. $C_{27}H_{23}O_2Cl_2Sb$ requires C, 56·7; H, 4·1%), and hydrogen sulphide in ethanol–ammonia reduced the dibromide to the *stibine*, m. p. 105—107° after recrystallisation from methanol containing a little ether (Found: C, 64·0; H, 4·6. $C_{27}H_{23}O_2Sb$ requires C, 64·7; H, 4·6%). This was used to seed the main reaction product and a semisolid mass resulted, which on trituration with methanol and ether gave the crude stibine (7·3 g.). Two recrystallisations of this from methanol containing a little ether gave the pure stibine (5·5 g.).

p-Carboxyphenyl-2-diphenylylphenylstibine.—The ester (4·0 g.) was hydrolysed by boiling 4% alcoholic potassium hydroxide (100 ml.) for ½ hr., then the solution was poured into water and acidified (Congo-red) with dilute hydrochloric acid. The precipitated *acid* (3·5 g.) had m. p. <100° and contained water, despite drying for prolonged periods at room temperature, but separated from absolute ethanol in rosettes of small needles, m. p. 199—200° (Found: C, 63·4; H, 4·1; Sb, 25·5. $C_{25}H_{19}O_2Sb$ requires C, 63·45; H, 4·05; Sb, 25·7%).

Optical Resolution of p-Carboxyphenylphenyl-p-tolylstibine.—Small-scale experiments indicated that combination of this acid with strychnine, brucine, and ephedrine gave rather soluble salts which separated as gums, but with (+)-1-phenylethylamine a solid was obtained. The first resolution was carried out as follows: the acid (2·8 g.) was suspended in warm acetone (20 ml.) and the addition of (+)-1-phenylethylamine (1 g.) gave a solution which, when kept overnight, deposited a first fraction of salt, $[\alpha]_D$ +2·1° (2·7 g.). This crystallised as rosettes of very small needles covered with a gel-like deposit. Evaporation of the mother-liquor provided a second fraction, $[\alpha]_D$ +16·6° (0·7 g.), which separated initially as a gel, but crystallised overnight. Recrystallisation of the first fraction, twice from acetone and once from ethanol, gave pure (−)-*acid* (+)-*base salt*, m. p. 174—176°, $[\alpha]_D$ −28·6° (0·35 g.) (Found: C, 65·4; H, 5·4. $C_{25}H_{19}O_2Sb,C_8H_{11}N,\frac{1}{2}H_2O$ requires C, 65·7; H, 5·3%). Two recrystallisations of the second fraction from ethanol gave (+)-*acid* (+)-*base salt*, m. p. 168—170°, $[\alpha]_D$ +46·6° (Found: C, 66·9; H, 5·1. $C_{25}H_{19}O_2Sb,C_8H_{11}N$ requires C, 66·7; H, 5·1%). Rotations were measured in "AnalaR" chloroform (l = 2, c ~0·25). Ethanol could not be used in place of acetone in the preparation of the salt, because the mixture of diastereoisomerides was too soluble in this solvent but, after a partial separation through acetone, alcohol was an efficient solvent for the final crystallisations.

In a second resolution, the acid (2·3 g.) and (+)-1-phenylethylamine (1·2 g.) were dissolved together in acetone (16 ml.). The first fraction of salt, F1 (2·3 g.), was filtered off after 24 hr., and a second, F2 (0·7 g.), after a further 48 hr. F1 was extracted with hot acetone (10 ml.), and the residue, after one recrystallisation from alcohol, gave pure (−)-acid (+)-base salt, $[\alpha]_D$ −28·8°, unchanged by further crystallisation. The acetone extract of F1 was used as solvent for the recrystallisation of F2, and the resultant salt (1·2 g.) had $[\alpha]_D$ +22·1°. This was recrystallised twice from alcohol and gave 0·3 g. of (+)-acid (+)-base salt, $[\alpha]_D$ +46·9°.

Isolation of (+)- and (−)-Acids.—The salt, $[\alpha]_D$ −28·8° (0·5 g.), was dissolved in ethanol (20 ml.), cooled to −10°, decomposed with 0·1N-sulphuric acid (20 ml.), and treated with water (20 ml.) to complete precipitation. The (−)-*acid*, dried *in vacuo* at room temperature, had m. p. 76—79°, $[\alpha]_D^{20}$ −46·9° (*c* 0·245 in pyridine) (Found: C, 63·2; H, 4·0%).

Similar treatment of the (+)-acid (+)-base salt gave the (+)-*acid*, m. p. 76—80°, $[\alpha]_D^{20}$ +47·2° (*c*, 0·223 in pyridine) (Found: C, 63·1; H, 3·9%). Attempts to crystallise the (−)-acid showed that it was much more soluble than the (±)-form in common organic solvents, from which it separated as a gum. No satisfactory solvent for crystallisation was found. Aqueous ethanol provided a specimen which was not characteristically crystalline (m. p. 135—139°) and this had $[\alpha]_D^{22}$ −40·4° (*c* 0·285 in "AnalaR" chloroform), a value almost identical with that shown by the original specimen, m. p. 76—79°.

Specific rotations in various solvents and the results of attempted racemisations are in Table 1. Freshly distilled thiophen-free toluene, b. p. 110°, *p*-xylene (99·6% pure), b. p. 138°, and decalin, b. p. 188—189°, were used in racemisation attempts. The rotation solutions in toluene and *p*-xylene were boiled under reflux (with precautions against loss of solvent), then cooled rapidly and examined at the temperatures stated. Readings were taken at half-hourly intervals and the maximum change observed was an increase of 0·005° in the rotation of the toluene solution.

A solution of the (−)-acid in decalin, α_D^{23} −0·48°, was boiled for 30 min. and when cooled

TABLE 1.

Wt. (g.) of acid in 20 ml.	Solvent	$[\alpha]_D$	Temp.	Optical stability of solution
0·0490	Pyridine	−46·9°	20°	Stable at 20°
0·0445	Pyridine	+47·2°	20°	Stable at 20°
0·0467	Chloroform	−40·7°	22°	Stable at 22°
0·0453	Toluene	−57·4°	18°	Stable on boiling (1 hr.)
0·1032	*p*-Xylene	−52·3°	18°	Stable on boiling (2 hr.)
0·1020	Decalin	−47·1°	23°	Oxidised on boiling

deposited a solid, m. p. 290—294°. The filtrate had α_D^{23} −0·22°, and this fell to α_D^{23} −0·03° after a total of 105 minutes' boiling. The solid was the *stibine oxide* (Found: C, 61·2; H, 4·1. $C_{25}H_{19}O_2Sb$ requires C, 61·4; H, 3·9%).

The rotation of a solution of the (−)-acid in chloroform was unaffected by a trace of hydrochloric acid, but on introduction of 0·5 ml. of chloroform through which dry hydrogen chloride had been passed for ½ min., the rotation fell from α_D^{20} −0·20° to −0·02° in 26 hr. Removal of

TABLE 2.

Compound	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
Triphenylstibine	2540—2550	12,800	2400	8920
(II; R = Ph, R′ = Me)	2500—2550	16,000	(Inflection)	
9-*p*-Tolyl-9-stibiafluorene	2870	12,400	2770	11,000

the chloroform left a residue which had the characteristic smell of diphenyl and was separated by alkali into an acidic fraction and impure diphenyl, m. p. and mixed m. p. 65—69°. The acidic fraction was not identified.

Absorption Spectra.—These were determined in 95% ethanol (see Table 2 and Fig. 2).

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cyclo*Hexane Derivatives. Part I. Preparation of* cis- *and* trans-3 : 3 : 5-*Trimethylcyclohexanol and Proof of Configuration.*

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The *cis*- and the *trans*-isomer of 3 : 3 : 5-trimethyl*cyclo*hexanol have been isolated in the pure state and several of their derivatives prepared; the melting point–composition relation of the isomeric alcohols has been studied, and configurations have been assigned to them on the basis of their relative stability and infrared spectra; the isomer of m. p. 57·3° is considered to be the *trans*-, and that of m. p. 37·3 to be the *cis*-form.

Considerable confusion exists as to the identity and configuration of *cis*- and *trans*-3 : 3 : 5-trimethyl*cyclo*hexanol (see Table 1). Pure isomers were required for work on the mechanism of reductions of cyclic compounds, also unassailable assignment of configurations.

Table 1. *Summary of previous methods of preparation and properties of* 3 : 3 : 5-*trimethyl*cyclo*hexanol,*

Starting material	Reagent	M. p. of product	Configuration assigned	Yield (%)
(*a*) *iso*Phorone	Moist Et_2O–Na	37°	*trans* [b]	—
(*b*) *iso*Phorone	Na–EtOH	34·5	*trans*	70—75
(*c*) Dihydro*iso*phorone	H_2–Pt in AcOH	52	—	—
(*d*) *iso*Phorone	H_2–Adkins' catalyst	58·5	[a]	—
(*e*) *iso*Phorone	H_2–Pt	58·5—59·0	—	—
(*f*) *iso*Phorone	H_2–Ni	—	—	~100%
(*g*) *iso*Phorone	H_2–catalyst	—	—	98
(*h*) Dihydro*iso*phorone	$LiAlH_4$ in Et_2O	Oil	*cis*	85
(*i*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 34·5°)	Isomerisation with Zn–HCl–AcOH	Oil	*cis*	—

[a] Considered to be identical with products from (*a*) and (*b*).
[b] Kerp, *Annalen*, 1896, **290**, 139. [c] Knoevenagel and Fischer, *ibid.*, 1897, **297**, 194. [d] Skita and Meyer, *Ber.*, 1912, **45**, 3593. [e] Morgan and Hardy, *Chem. and Ind.*, 1933, 518. [f] Dodge and Kremers, *J. Amer. Pharm. Assoc.*, 1942, **31**, 527. [g] Birch and Johnson, *J.*, 1951, 1493. [h] Ipatiev, Germain, and Pines, *Bull. Soc. chim. France*, 1951, 259. [i] Braude and Evans, *J.*, 1954, 607. [j] As (*b*).

This led us to re-investigate the hydrogenation of *iso*phorone. By a combination of fractional distillation and crystallisation of the mixtures resulting after the use of a reduced nickel catalyst, we have obtained isomers of 3 : 3 : 5-trimethyl*cyclo*hexanol of m. p. 57·3°, b. p. 76°/10 mm., and m. p. 37·3°, b. p. 85°/10 mm., and characterised them by a number of derivatives (see Table 2); a melting point–composition diagram of the two isomers has

Table 2. *M.p.s of* cis- *and* trans-3 : 3 : 5-*trimethyl*cyclo*hexanol and its derivatives.*

	cis	*trans*		*cis*	*trans*
Alcohol	37·3°	57·3°	Hydrogen phthalate ...	129°	122·5°
α-Naphthylurethane	71	132	Phthalate	93	57
3 : 5-Dinitrobenzoate † ...	71	98			

† Dodge and Kremers (*loc. cit.*) described a 3 : 5-dinitrobenzoate, m. p. 98·5—99°, prepared from their alcohol of m. p. 58·5—59°; no analysis was reported. From their commercial "*iso*phoronyl alcohols" they prepared another two products described as 3 : 5-dinitrobenzoates, again without analytical figures, of m. p. 61·5—63° and 71·5—72·5°. Braude and Evans (*loc. cit.*) isolated from their liquid product a 3 : 5-dinitrobenzoate, m. p. 71°, which may have been a stereochemically pure ester.

been used to analyse the products obtained in this work. The isomer of higher m. p. is much less soluble in all the usual organic solvents than the other isomer, which is extremely soluble; mixtures containing not less than 30% of the other form are

difficult to separate by crystallisation or simple distillation. It seems that earlier workers have, in general, isolated the higher-melting isomer admixed with varying amounts of the other.

Reductions with sodium and alcohol in this laboratory have given total products of m. p. 26°, containing 37% of high- and 63% of low-melting isomer;* thus, the products isolated by Kerp, and by Knoevenagel and Fischer, must have been mixtures containing about 65% of high- and 35% of low-melting isomer.

An experiment by Morgan and Hardy's method gave a mixture containing about 70% of the low-melting isomer although the other form was the isomer isolated after extensive recrystallisation. The product isolated by Dodge and Kremers was the pure high-melting isomer; Skita and Meyer's was mainly the high- containing about 15% of the low-melting isomer. Since all the mixtures melt at not below 20°, the liquid product isolated by Braude and Evans cannot have been a pure isomer. Work in these laboratories has shown that reduction of dihydro*iso*phorone by lithium aluminium hydride gives a 1 : 1 mixture of *cis*- and *trans*-isomers.*

The isomer of m. p. 37·3° which we have isolated therefore does not appear to have been described previously. It is suitably prepared (*ca.* 70% of the total product) by hydrogenation of *iso*phorone with nickel catalyst at about 130°/100 lb. per sq. in. On the other hand similar hydrogenation at room temperature gives a crude product containing up to 90% of the high-melting isomer. We found that in the presence of nickel catalyst and hydrogen either isomer can be epimerised to a mixture of the two; at equilibrium the isomer of lower m. p. preponderates and it would therefore be expected, from the work of Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), of Beckett, Pitzer, and Spitzer, (*J. Amer. Chem. Soc.*, 1947, **69**, 2488), and of many later workers, that this, the more stable isomer, is the *cis*-form. In *cis*-1 : 3-disubstituted *cyclo*hexanes the two substituents are both in relatively unhindered equatorial positions and, when one of these is a hydroxyl group, the tendency for intermolecular hydrogen bonding would be expected to be much greater than in the corresponding *trans*-compound. We prepared pure *cis*- and *trans*-3-methyl*cyclo*hexanol as reference compounds since their configuration has been unequivocally established (Goering and Serres, *ibid.*, 1952, **74**, 5908; Noyce and Denney, *ibid.*, p. 5912). The infrared spectra (Table 3) show that, as postulated, the intensity of

TABLE 3. *Optical density of two infrared bands of* cis- *and* trans-*isomers.*

		3-Methyl*cyclo*hexanol				3 : 3 : 5-Trimethyl*cyclo*hexanol			
Concn.	Cell	*cis*		*trans*		M. p. 37·3°		M. p. 57·3°	
(%)	(mm.)	2·75 μ	2·9 μ	2·75 μ	2·9 μ	2·75 μ	2·9 μ	2·75 μ	2·9 μ
5	0·5	0·099	0·984	0·130	0·640	0·096	0·795	0·154	0·361
1	10	0·286	0·602	0·324	0·434	0·350	0·480	0·380	0·288
0·25	10	0·195	0·030	0·203	0·018	0·208	0·027	0·213	0·012

absorption at 2·9 (hydrogen-bonded hydroxyl) relative to that at 2·75 μ (unassociated hydroxyl) is markedly greater in the *cis*- than in the *trans*-compound; a similar difference exists in the spectra of the isomers of 3 : 3 : 5-trimethyl*cyclo*hexanol; here, owing to the proximity of the associated and unassociated hydroxyl bands and their consequent interaction, it proved impossible to measure optical densities with a high absolute accuracy, but relative values at any one concentration illustrate the stronger association in the *cis*-compounds and we conclude that the isomers of m. p. 37·3° and 57·3° are respectively *cis*- and *trans*-3 : 3 : 5-trimethylcyclohexanol.† No relation appears to exist between configuration and m. p. of these alcohols and their derivatives (see Table 2).

* These and other non-catalytic reductions will be described in a later paper.

† Pickett and Ungnade (*J. Amer. Chem. Soc.*, 1949, **71**, 1311) showed that the intensity of infrared absorption due to the associated hydroxyl group is greater in the *trans*- than in the *cis*-isomer of 4-phenyl- and 4-*cyclo*hexyl-*cyclo*hexanol and attributed this to some form of steric inhibition; the reason for this inhibition is undoubtedly the same as that given for the compounds described above, except, of course, that in the case of 2- and 4-substituted *cyclo*hexanols it is the *cis*-, and not the *trans*-isomers in which the hydroxyl group occupies the hindered axial position. The infrared method thus appears capable of differentiating *cis*- and *trans*-isomers of substituted *cyclo*hexanols.

Experimental

M. p.s of the isomeric alcohols and mixtures of them were determined by a standard cooling-curve method and are corrected, those of the derivatives of the alcohols by the usual capillary-tube method and are uncorrected. Unless otherwise stated, light petroleum had b. p. 60—80°.

*iso*Phorone was obtained by fractionally distilling commercial material through a column packed with 4-mm. Fenske glass helices (approx. 15 theoretical plates); fractions of constant n_D^{20} (1·478) were collected.

Preparation of trans-3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—*iso*Phorone (138 g.) in methanol (100 ml.) was hydrogenated at room temperature and 100 lb. per sq. in. with a commercial reduced nickel catalyst (7 g.) for 16 hr.; the catalyst was filtered off and washed with methanol. Methanol was distilled off, finally under a vacuum. A colourless crystalline product, m. p. 53—54° (132 g., 93%), was obtained; the m. p. indicated a composition of 86—88% of *trans*-isomer. Analysis by the hydroxylamine method showed less than 1% of ketone calculated as *iso*phorone. This product was recrystallised from light petroleum and then from ethylene dichloride several times until a product of high purity, as indicated by cooling-curve determination, was obtained. The purest sample obtained by this means had m. p. 57·3°, b. p. 76°/10 mm., and gave an *α-naphthylurethane* [from light petroleum (b. p. 80—100°)] (Found: C, 77·1; H, 8·2; N, 4·8. $C_{20}H_{23}O_2N$ requires C, 77·1; H, 8·1; N, 4·5%), *hydrogen phthalate* (from absolute alcohol) (Found: C, 70·6; H, 7·7. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%), *phthalate* (from aqueous alcohol) (Found: C, 75·4; H, 9·4. $C_{25}H_{38}O_4$ requires C, 75·3; H, 9·2%), and 3 : 5-*dinitrobenzoate* (from 95% alcohol) (Found: C, 56·9; H, 6·0; N, 7·9. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0; N, 8·3%) (for m. p.s see Table 2).

Preparation of cis-3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—*iso*Phorone (138 g.) was hydrogenated at 130°/100 lb. per sq. in. with a commercial reduced nickel catalyst (7 g.) and, after the absorption of hydrogen ceased (5 hr.), stirring and heating were continued for a further 9 hr. The catalyst was filtered off; the filtrate solidified to a crystalline solid, m. p. 27° (133 g., 94%), containing 70% of *cis*-isomer and less than 0·5% of ketone. This product was fractionally distilled through a packed column (Fenske helices, 15 theoretical plates) with a reflux ratio of 25 : 1.1 Fractions were tested at intervals and those with a cooling curve indicating high purity were combined. The purest material so obtained had m. p. 37·3°, b. p. 86°/10 mm., and gave an *α-naphthylurethane* [from light petroleum (b. p. 80—100°)] (Found: C, 76·8; H, 8·5; N, 4·7%), *hydrogen phthalate* (from acetic acid) (Found: C, 69·9; H, 7·7%), *phthalate* (from absolute alcohol) (Found: C, 75·3; H, 9·2%), and 3 : 5-*dinitrobenzoate* (from 95% alcohol) (Found: C, 57·1; H, 6·3; N, 8·35%) (m. p.s in Table 2).

Melting Point–Composition Curve.—This was constructed from m. p.s determined by the cooling-curve method, using known mixtures of the above two pure isomers. Table 4 illustrates the figures.

Table 4. *Melting points of mixtures of* cis- *and* trans-3 : 3 : 5-*trimethyl*cyclo*hexanol*.

Trans (%)	100	95	90	80	70	60	55	50	47·5	40	30	20	10	5	0
M. p.	57·3°	56·8°	55·0°	49·0°	41·5°	32·5°	27·0°	20·0°	21·0°	24·0°	26·8°	30·5°	33·5°	35·5°	37·3°

Isomerisation of 3 : 3 : 5-*Trimethyl*cyclo*hexanol*.—(*a*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 54°; 10 g.), containing 88% of *trans*-isomer, and commercial reduced nickel catalyst (0·5 g.) were shaken in an autoclave under hydrogen at 130°/100 lb. per sq. in. for 9 hr. The catalyst was removed. The product had m. p. 27° and contained 70% of *cis*-isomer. Analysis by the hydroxylamine method showed that less than 0·5% of ketone was present.

(*b*) 3 : 3 : 5-Trimethyl*cyclo*hexanol (m. p. 35·2°; 5 g.), containing 95% of *cis*-isomer, and commercial reduced nickel catalyst (0·25 g.) were treated as in (*a*) at 140° for 9 hr. The resulting product had m. p. 28° and contained 73% of *cis*-isomer; its ketone content was less than 0·5%.

Hydrogenation of iso*Phorone by Morgan and Hardy's Method* (loc. cit.).—*iso*Phorone (276 g.) was hydrogenated at 160°/1500 lb. per sq. in. with Adkins's copper–barium chromite catalyst (*J. Amer. Chem. Soc.*, 1932, **54**, 1139) (10 g.) for 10 hr. The catalyst was filtered off; the filtrate solidified, had m. p. 27° (268 g., 94%), and contained 70% of *cis*-isomer. Analysis by the hydroxylamine method showed that less than 0·5% of ketone was present.

Preparation of trans-3-*Methyl*cyclo*hexanol*.—3-Methyl*cyclo*hexanone (50 g.) was hydrogenated with commercial nickel catalyst (2·5 g.) at room temperature and 100 lb. per sq. in. until hydrogen absorption ceased (2 hr.). The catalyst was filtered off; the resultant 3-methyl-*cyclo*hexanol had d_4^{20} 0·9122 and thus contained 77% of *trans*-isomer, according to the figures

given by Macbeth and Mills (*J.*, 1945, 709), transposed to allow for the later reversal of the configuration there assigned to the two isomers.

This 3-methyl*cyclo*hexanol (26 g.) was heated with 3 : 5-dinitrobenzoyl chloride (54 g.) at 130° for 30 min. and the product recrystallised from light petroleum several times, to give the 3 : 5-dinitrobenzoate, m. p. 99°, of the *cis*-alcohol. The mother-liquors gave a residue which, recrystallised four times from methanol, gave impure *cis*-3 : 5-dinitrobenzoate, m. p. 94—98° (mixed m. p. with the *trans*-dinitrobenzoate, 80°). The mother-liquors from the methanol recrystallisations were evaporated and the residue was recrystallised four times from light petroleum, to give the 3 : 5-dinitrobenzoate, m. p. 108—111°, of the *trans*-alcohol.

The *trans*-ester (10 g.) was refluxed with potassium hydroxide (3 g.) in water (25 ml.) and ethanol (250 ml.) for 24 hr. Dilution with water, extraction with ether, evaporation of the extract, steam-distillation of the residue, and extraction of the distillate with light petroleum (b. p. 40—60°) gave *trans*-3-methyl*cyclo*hexanol, b. p. 170—171°/772 mm., n_D^{20} 1·4581 (Macbeth and Mills, *loc. cit.*, give n_D^{20} 1·4583).

Preparation of cis-3-*Methyl*cyclo*hexanol.*—*m*-Cresol (100 g.) was hydrogenated with commercial nickel catalyst (5 g.) at 160°/100 lb. per sq. in. The resultant 3-methyl*cyclo*hexanol had d_4^{20} 0·9101 and thus contained 55% of *cis*-isomer. This material (62 g.) was heated with phthalic anhydride (74 g.) on the steam-bath for 24 hr. The product was poured into an excess of 10% aqueous sodium carbonate solution and stirred until dissolved. The aqueous solution was extracted twice with benzene and then aerated until no smell of benzene remained. The aqueous phase was then acidified and extracted with chloroform; after removal of chloroform, the crude product (100 g.) was treated with light petroleum and cooled in acetone–solid carbon dioxide; the precipitated solid, recrystallised from light petroleum, gave pure *cis*-3-methyl-*cyclo*hexyl hydrogen phthalate, m. p. 94°.

This ester (10 g.) was refluxed with potassium hydroxide (3 g.) in water (25 ml.) and ethanol (250 ml.) for 48 hr. The ethanol was distilled off *in vacuo* from the steam-bath, and the 3-methyl*cyclo*hexanol steam-distilled. The distillate was extracted with light petroleum and the final product distilled, giving *cis*-3-methyl*cyclo*hexanol, b. p. 175°/777 mm., n_D^{20} 1·4579 (Macbeth and Mills, *loc. cit.*, report n_D^{20} 1·4573). Hydrolysis of the ester was later found to proceed satisfactorily in the absence of ethanol and the product could then be directly steam-distilled.

Measurement of Infrared Spectra.—These were determined in CCl_4 solution with a Hilger D. 209 infrared spectrometer with a modified double-beam system (Hales, *J. Sci. Instr.*, 1953, **30**, 52).

We are indebted to Mr. Hales and Mr. Kynaston, of the Chemical Research Laboratory, Teddington, for the infrared measurements and for discussions regarding their interpretation, to Mr. K. D. Hardy of this laboratory for the preparation of the derivatives described in Table 2, and to the Directors of Messrs. Howards of Ilford, Ltd., for permission to publish this work.

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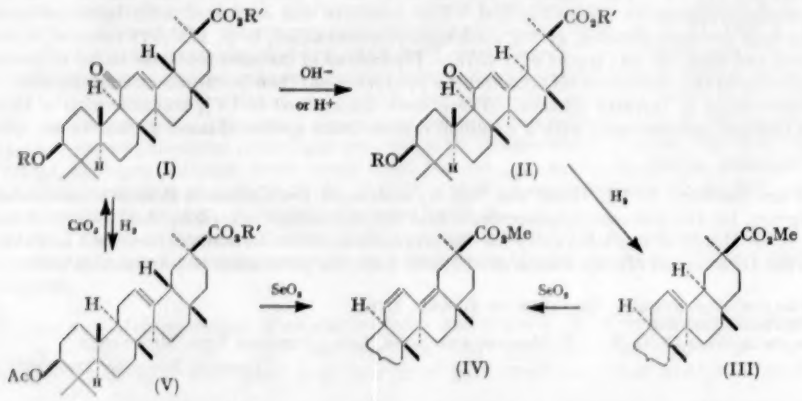
Triterpenoids. Part XLII. The Configuration of the Carboxyl Group in Glycyrrhetic Acid.*

By J. M. Beaton and F. S. Spring.

[Reprint Order No. 6311.]

18α-Glycyrrhetic acid (II; R = R′ = H) has been prepared and characterised. A comparison of the rates of alkaline hydrolysis of methyl glycyrrhetate (I; R = H, R′ = Me) and methyl 18α-glycyrrhetate (II; R = H, R′ = Me) shows that the carboxyl group in glycyrrhetic acid is axially bound and therefore β-orientated.†

The constitution of glycyrrhetic acid was established by the elegant researches of Ruzicka, Jeger, and their collaborators (Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804; Ruzicka, Leuenberger, and Schellenberg, *ibid.*, p. 1271; Ruzicka and Marxer, *ibid.*, 1939, **22**, 195; Ruzicka and Jeger, *ibid.*, 1942, **25**, 775; Ruzicka, Jeger, and Winter, *ibid.*, 1943, **26**, 265; Ruzicka, Jeger, and Ingold, *ibid.*, p. 2278). The stereochemistry of the acid, apart from the configuration of the carboxyl group, is disclosed by its conversion (Ruzicka and Marxer, *loc. cit.*) into β-amyrin, the stereochemistry of which has been fully elucidated mainly by Barton and Holness (*J.*, 1952, **78**; cf. Barton, *J.*, 1953, 1027). The experiments described in the present paper establish that the carboxyl group in glycyrrhetic acid is β-orientated and so lead to the complete definition shown in (I; R = R′ = H).



Prolonged treatment of methyl glycyrrhetate with concentrated alkali gives an acid different from, and isomeric with, glycyrrhetic acid. The isomeric acid is also obtained by heating a solution of glycyrrhetic acid in acetic acid containing concentrated hydrochloric acid. It has been characterised by the preparation of its acetate, its methyl ester, and its methyl ester acetate. Like glycyrrhetic acid, the isomer shows the characteristic

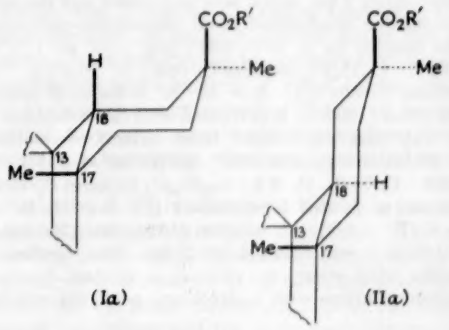
* Part XLI, *J.*, 1955, **3072**.

† We suggest that the numbering of the oleanane carbon skeleton should now be extended to that shown opposite. The α-carbon atoms attached to $C_{(4)}$ and $C_{(8)}$ are given the lower numbers, 23 and 29 respectively, and the β-carbon atoms attached at the same points are given the higher numbers, 24 and 30 respectively. This conforms with the numbering hitherto used for 23- and 24-substituted oleanane derivatives (Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 2321). This system being used, the proof given in the present paper that the carboxyl group in glycyrrhetic acid is β-orientated leads to the systematic name 3β-hydroxy-11-oxo-olean-12-en-30-oic acid for this compound and so does not necessitate a change from previous practice.

ultraviolet absorption of an αβ-unsaturated ketone. The behaviour of the analogously constituted methyl 11-oxo-oleanolate acetate (Barton and Holness, *loc. cit.*) and 11-oxo-olean-12-enyl benzoate (Budziarek, Manson, and Spring, *J.*, 1951, 3336) with concentrated alkali is a *prima facie* reason for assuming that the isomeric acid differs from glycyrrhetic acid only in the configuration at $C_{(18)}$ and that the configuration at $C_{(9)}$ in the two acids is the same. A proof that the isomeric acid is 18α-glycyrrhetic acid (II; R = R′ = H) was obtained by hydrogenolysis of the methyl ester acetate (II; R = Ac, R′ = Me) which yielded the 11-deoxo-compound (III); oxidation of this with selenium dioxide gave the methyl 11 : 13(18)-dienolate acetate (IV) previously obtained by similar oxidation of methyl deoxoglycyrrhetate acetate (V; R′ = Me) (Bilham, Kon, and Ross, *J.*, 1942, 535; Ruzicka and Jeger, *loc. cit.*; Barton and Brooks, *J.*, 1951, 257).

It is possible that variations observed in the constants of glycyrrhetic acid and its derivatives, such as those which led Voss, Klein, and Sauer (*Ber.*, 1937, **70**, 122; cf. Ruzicka, Furter, and Leuenberger, *Helv. Chim. Acta*, 1937, **20**, 312) to postulate the existence of α- and β-glycyrrhetic acids, may in part be due to the formation of mixtures of glycyrrhetic and 18α-glycyrrhetic acid.

Comparative hydrolyses of methyl glycyrrhetate and 18α-glycyrrhetate show that the former is much more hindered than the latter. For example, the 18α-ester with boiling 3% alcoholic potassium hydroxide gives a 91·5% yield of the 18α-acid in 2 hours, while methyl glycyrrhetate gives only a 5% yield of glycyrrhetic acid, the remainder being unchanged ester. In our opinion, this proves that the carboxyl groups of glycyrrhetic and of 18α-glycyrrhetic acids are respectively axial and equatorial. This means that the carboxyl group of glycyrrhetic acid (I*a*) is β-orientated, the change to 18α-glycyrrhetic acid (II*a*) leading to a conformation in which the β-carboxyl group is equatorial.



(I*a*) (II*a*)

It has been reported that oxidation of deoxoglycyrrhetic acid acetate (V; R′ = H) with chromic acid gives a neutral and an acidic product in approximately equal proportions. The acidic product was identified as glycyrrhetic acid acetate (I; R′ = H; R = Ac). The neutral compound was formulated as a saturated keto-lactone and its formation was used as a proof of the close proximity of the double bond and the carboxyl group in deoxoglycyrrhetic acid (Ruzicka and Marxer, *loc. cit.*). The formation of a saturated keto-lactone from (V; R′ = H) is, on steric considerations, remarkable and the oxidation of deoxoglycyrrhetic acid acetate was therefore re-examined. We have been unable to obtain the saturated keto-lactone, the oxidation giving glycyrrhetic acid acetate in high yield as sole product. The reason for this discrepancy, in our view, is that it is difficult completely to extract glycyrrhetic acid acetate from ether with either sodium hydrogen carbonate or with sodium carbonate—the latter ("soda") was used in the original experiment; rapid and complete extraction requires the use of caustic alkali. After extraction of an ethereal solution of the reaction product with sodium carbonate solution, we obtained a "neutral" fraction which was in fact glycyrrhetic acid acetate; a comparison of the constants of glycyrrhetic acid acetate and the "saturated keto-lactone" reported

by Ruzicka and Marxer (and shown below), together with our experience, shows that these compounds are identical.

Glycyrrhetic acid acetate	$C_{32}H_{48}O_5$, m. p. 322—325°, $[\alpha]_D$ +141°
" Saturated keto-lactone "	$C_{32}H_{48}O_5$, m. p. 319—322° (sinters 308°), $[\alpha]_D$ + 134°

Experimental

Specific rotations were measured in $CHCl_3$ and ultra-violet absorption spectra in EtOH.

18α-Glycyrrhetic Acid (II; R = R′ = H).—(*a*) A mixture of methyl glycyrrhetate (I; R = H, R′ = Me) (10 g.) and potassium hydroxide (400 g.) in water (200 c.c.) and ethanol (1800 c.c.) was refluxed for 120 hr. The solution was diluted with water (2 l.), then acidified with concentrated hydrochloric acid, and the precipitated solid collected. Repeated crystallisation from chloroform–methanol yielded *18α-glycyrrhetic acid* (3·8 g.) as rectangular plates, m. p. 331—335°, $[\alpha]_D$ + 98° ± 4° (*c*, 0·13, 0·12), $\lambda_{max.}$ 2420 Å (ε 12,200). The acid is sparingly soluble in chloroform (Found: C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). (*b*) A solution of glycyrrhetic acid (1·5 g.) in acetic acid (50 c.c.) containing concentrated hydrochloric acid (10 c.c.) was heated on the steam-bath for 2 hr., during which a small amount of crystals separated. Water was added and the product crystallised repeatedly from chloroform–methanol to give 18α-glycyrrhetic acid (0·6 g.) as plates, m. p. 330—335° (no depression).

18α-Glycyrrhetic Acid Acetate (II; R = Ac, R′ = H).—18α-Glycyrrhetic acid (0·65 g.) was heated with pyridine and acetic anhydride on the steam-bath for 1½ hr. The product crystallised from chloroform–methanol, to give *18α-glycyrrhetic acid acetate* (0·50 g.) as triangular plates, m. p. 321—323°, $[\alpha]_D$ + 91° (*c*, 1·9), $\lambda_{max.}$ 2430 Å (ε 11,900) (Found: C, 75·2; H, 9·6. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%).

Methyl 18α-Glycyrrhetate (II; R = H, R′ = Me).—Diazomethane in ether was added to a suspension of 18α-glycyrrhetic acid (1·0 g.) in methanol (200 c.c.) until the solid dissolved and a yellow colour persisted. After 1 hr., acetic acid was added and the mixture evaporated under reduced pressure. The residue crystallised from chloroform–methanol, to give *methyl 18α-glycyrrhetate* (0·75 g.) as needles, m. p. 267—268°, $[\alpha]_D$ +95° (*c*, 1·7), $\lambda_{max.}$ 2440 Å (ε 11,300) (Found: C, 77·0; H, 10·2. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

Methyl 18α-Glycyrrhetate Acetate (II; R = Ac, R′ = Me).—A solution of 18α-glycyrrhetic acid acetate (350 mg.) in ether (100 c.c.) was treated with diazomethane in ether. The product, isolated in the usual way and crystallised from chloroform–methanol, gave *methyl 18α-glycyrrhetate acetate* as plates, m. p. 254—255° (softening at 245°), $[\alpha]_D$ +87° (*c*, 1·4), $\lambda_{max.}$ 2430 Å (ε 12,000) (Found: C, 75·2; H, 9·5. $C_{33}H_{50}O_5$ requires C, 75·2; H, 9·6%).

Comparative Hydrolyses of Methyl Glycyrrhetate (I; R = H, R′ = Me) *and Methyl 18α-Glycyrrhetate* (II; R = H, R′ = Me).—A solution of the ester (200 mg.) in aqueous-methanolic potassium hydroxide (100 c.c.) was refluxed for 2 hr. The solution was diluted with water and extracted repeatedly with ether, so yielding a neutral fraction of unchanged ester. Acidification of the alkaline solution with hydrochloric acid, followed by ether extraction, gave the acid fraction:

Concn. (%) of alkali	1	3	5 *
Acid (%) from: Me glycyrrhetate	0	5	37
Me 18α-glycyrrhetate	28·5	91·5	98

* The methyl ester acetates were used in this case and the refluxing period was 2½ hr.

The acid fraction from the hydrolysis of methyl 18α-glycyrrhetate by 3% alcoholic potassium hydroxide crystallised from chloroform–methanol, to give 18α-glycyrrhetic acid as plates, m. p. 331—335°, $[\alpha]_D$ +100° ± 4° (*c*, 0·12).

Hydrogenolysis of Methyl 18α-Glycyrrhetate Acetate (II; R = Ac, R′ = Me).—A solution of the keto-ester (500 mg.) in glacial acetic acid (150 c.c.) was shaken with platinum and hydrogen until absorption was complete (*ca.* 36 hr.). The product, isolated in the usual way and crystallised from chloroform–methanol, yielded *methyl 11-deoxo-18α-glycyrrhetate acetate* (III) as plates (460 mg.), m. p. 242—243°, $[\alpha]_D$ +69° (*c*, 1·9), ε at 2060 Å = 2700 (Found: C, 77·7; H, 10·5. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). It gives a yellow colour with tetranitromethane.

Oxidation of Methyl 11-Deoxo-18α-Glycyrrhetate Acetate (III) *with Selenium Dioxide.*—A mixture of the methyl ester (300 mg.) in acetic acid (30 c.c.) was added to a suspension of selenium dioxide (300 mg.) in water (0·5 c.c.), and the mixture refluxed for 15 min., then

filtered. The filtrate was refluxed with zinc dust (*ca.* 1·5 g.) for 5 min. The product, isolated in the usual manner, crystallised from chloroform–methanol, to give methyl 3β-hydroxyoleana-11 : 13(18)-dien-30-oate acetate (IV) (235 mg.) which after recrystallisation from the same solvent had m. p. 234—235°, $[\alpha]_D$ − 34° (*c*, 2·2), $\lambda_{max.}$ 2410, 2500, and 2590 Å (ε 28,500, 32,200, and 19,800). A specimen prepared from methyl 11-deoxoglycyrrhetate acetate had m. p. 234—235° (no depression), $[\alpha]_D$ − 34° (*c*, 1·8).

We thank the Carnegie Trust for the Universities of Scotland for the award of a scholarship (to J. M. B.), and Dr. A. C. Syme and Mr. Wm. McCorkindale for the microanalyses.

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Kinetics of Nucleation in Supercooled Solutions.

By R. P. RASTOGI.

[Reprint Order No. 5809.]

The Volmer–Frenkel theory of nucleation has been extended to supersaturated solutions of solids in liquids. It has been shown that the surface free energy can be computed from the observed maximum rate of nucleation.

THE theory of nucleation in supercooled melts has been developed by Volmer ("Kinetik der Phasenbildung," T. Steinkopff, Dresden, 1939), Frenkel ("Kinetic Theory of Liquids," Oxford Univ. Press, 1946), and Dunning ("Crystal Growth," *Discuss. Faraday Soc.*, 1949, **5**, 83). The particular case of liquid solutions seems not to have received due attention although attempts have been made to consider two-dimensional crystallization in supercooled solutions (Rastogi and Chatterji, *J. Phys. Chem.*, 1955, **59**, 1). The object of the present paper is to develop a corresponding theory of nucleation for supercooled solutions, following Frenkel, to suggest a method for computing the interfacial tension at the crystal solution interface, a knowledge of which is essential for the understanding of any mechanism of nucleation.

Maximum Rate of Nucleation.—We shall assume that in a two-component system the solution contains crystal nuclei consisting only of the solute. The nuclei will be assumed to be spherical, corresponding to the smallest possible surface energy : though not strictly true for crystals, this assumption is reasonable for calculation of the surface area, for, as Pound and LaMer pointed out (*J. Amer. Chem. Soc.*, 1952, **74**, 2323), "the difference in area between the surface of the sphere and the more probable many-sided polyhedron is small."

Let μ_A and μ_B be the chemical potential of the solute in the liquid and the solid phase respectively. At the saturation point of the solution, the chemical potential of the solute in both the phases is the same. Let us suppose that at any temperature T ($T < T_s$), g molecules agglomerate to form a nucleus; the change in the Gibbs free energy can be expressed with reasonable accuracy as :

$$\Delta G = (\mu_B - \mu_A)g + \alpha g^{2/3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where α is linear in surface tension. Then the probability of nucleus formation will be given by :

$$W = C \exp\{(-1/kT)[g(\mu_B - \mu_A) + \alpha g^{2/3}]\} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It can be shown that

$$\mu_B - \mu_A \approx -(L_s/T_s)(T_s - T) + (\Delta\mu)_{T,P}$$

where L_s is the heat of solution and $(\Delta\mu)_{T,P}$ is the change in chemical potential with change

in concentration. If the change in concentration during the process of nucleation is assumed to be small, then

$$\mu_B - \mu_A \approx -(L_s/T_s)(T_s - T)$$

and W is given by

$$W = C \exp\{(-1/kT)[-g(T_s - T)(L_s/T_s) + \alpha g^{2/3}]\} \quad . \quad . \quad . \quad . \quad (4)$$

It is evident from equation (1) that ΔG increases as g increases, but later attains a maximum value and then decreases. The value of g for which ΔG is a maximum is given by

$$g_{max.} = \left[\frac{2}{3} \cdot \frac{\alpha T_s}{L_s(T_s - T)}\right]^3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

hence the rate of nucleus formation J is given by

$$J = C \exp\left\{-\frac{\alpha}{3kT}\left[\frac{\alpha}{3} \cdot \frac{\alpha T_s}{L_s(T_s - T)}\right]^2\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

In formation of three-dimensional nuclei from vapour, diffusion plays an insignificant rôle and is practically the same throughout the volume, but in supersaturated solutions the effect of diffusion becomes pronounced. For such cases, equation (6) has to be modified as follows :

$$J = C \exp\left\{-\frac{\alpha}{3kT}\left[\frac{2}{3} \cdot \frac{\alpha T_s}{L_s(T_s - T)}\right]^2 - \frac{\Delta u}{kT}\right\} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where Δu is the activation energy for diffusion, following Frenkel (*Sowjet Physik*, 1932, **1**, 498) and Becker (*Proc. Phys. Soc.*, 1940, **52**, 71). Expression (7) shows that when the degree of supersaturation is small the velocity is very small, but that it increases rapidly as T decreases until it attains a maximum value. The maximum value of J can be found as follows. Differentiating expression (7) with respect to T and putting dJ/dT equal to zero, we get

$$\frac{(T_s - T)^3}{T_s^2(3T - T_s)} = \frac{4}{27} \cdot \frac{\alpha^3}{L_s^2} \cdot \frac{1}{\Delta u} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

This equation should be satisfied when $T = T_{max.}$, the temperature at which the rate is maximum. If $T_s/T_{max.} = x$, equation (8) yields :

$$\frac{(x-1)^3}{x^2(3-x)} = \frac{4}{27} \cdot \frac{\alpha^3}{L_s^2} \cdot \frac{1}{\Delta u} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

The maximum rate is given by

$$J_{max.} = C \exp\left\{-\frac{\Delta u}{kT_{max.}}\left[1 + \frac{\alpha(x-1)}{(3-x)}\right]\right\} \quad . \quad . \quad . \quad . \quad . \quad (10)$$

When x is sufficiently close to 1, equations (9) and (10) yield :

$$(x-1)^3 = \frac{8}{27} \cdot \frac{\alpha^3}{L_s^2} \cdot \frac{1}{\Delta u}$$

and

$$J_{max.} = C \exp(-\Delta u/kT_{max.}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

It is clear from equations (7) and (9) that the temperature of maximum velocity is not so sensitive to the magnitude of the activation energy of self-diffusion as is the rate.

Computation of Interfacial Tension.—Attempts were made to measure the rate of formation of nuclei in supersaturated solutions but this was not achieved satisfactorily. Even

under controlled conditions, growth of the nuclei was the greatest disturbing factor. For nucleation in melts, these and other difficulties have been solved to a great extent by Vonnegut (*J. Colloid Sci.*, **1948**, **3**, 563) by a procedure based on the idea that, if the bulk liquid is subdivided into a great many tiny droplets isolated from each other, the more active foreign nuclei would be crowded into a few of the droplets and their effect would thus be confined in a small part of the total mass. It is doubtful whether this technique can be applied to nucleation in solution as the phase separation involves changes in concentration. The theory cannot be checked against experiment even if the rate could be determined experimentally, since the constant and the interfacial tensions are not known. However, equation (9) can be used to compute the value of interfacial free energy at the crystal–solution interface. A method for the estimation of this important quantity has been suggested by Pound and LaMer (*loc. cit.*), but there are limitations to their procedure. However, with the knowledge of temperature of maximum velocity alone, equation (9) can more conveniently yield the value of interfacial free energy. The experimental determination of $T_{max.}$ is not difficult. In fact Tammann has described a method (*Z anorg. Chem.*, **1914**, **87**, 248) in which a temperature gradient is generated in a tube filled with a supercooled melt; the point at which most crystals appear corresponds to the temperature of the maximum velocity of formation of nuclei.

Unfortunately no such data exist for solutions. Hence, it is difficult to get an accurate estimate of interfacial tensions at the crystal–solution interface. However, the lower limit of interfacial tensions can be calculated as follows. The temperature of maximum velocity can never be higher than that of spontaneous crystallization, because, however pure the solution may be, it is not possible to free it from foreign nucleation catalysts. Hence, if we use the temperature of spontaneous crystallization instead of the temperature of maximum velocity we can get the lower limit for the interfacial free energy from equation (9). We have tried to calculate " α " for several systems for which the data for temperature of spontaneous crystallization are available (Chatterji and Bose, *J. Indian Chem. Soc.*, **1949**, **26**, 283; **1943**, **20**, 183). The activation energy of self-diffusion was calculated from the viscosity data (*ibid.*, **1948**, **25**, 39) by using the relation $\eta = \text{Const. exp. } (\Delta u/kT)$, though this relation is strictly valid only for dilute solutions. The values of heats of solution were taken from International Critical Tables. In the absence of data, the heat of solution was taken to be equal to the heat of fusion. The calculated values of the minimum possible interfacial free energy for certain systems are given in the Table. These values seem to be

Computed values of interfacial free energy (solute, naphthalene).

Solvent	$\Delta u/k$ (cal.)	L_s (cal. mole^{-1})	x (obs.)	α (ergs)
Chlorobenzene	2390	4557	1·0133	43·35
Benzene	2672	4421	1·017	58·84
Toluene	2184	4270	1·02	63·14
Hexane	1864	4557	1·0266	82·90
Aniline	4352	4731	1·03	127·00

somewhat high, although by using the Ostwald–Freundlich equation very much higher values have been obtained for calcium and barium sulphates (cf. Jones, *Z. physikal. Chem.*, **1913**, **82**, 448; Dundon and Mack, *J. Amer. Chem. Soc.*, **1923**, **45**, 485). It may be stressed that the above calculations are correct, subject to the limitations of the theory which uses the concept of quasi-equilibrium.

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The Chemistry of Dammar Resin.

By J. S. Mills and A. E. A. Werner.

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By the use of column and reversed-phase paper chromatography a thorough analysis of dammar resin has been made. The "β-resene" has been shown to be a polymeric material, while the remainder of the resin is principally a complex mixture of neutral and acidic triterpenes, some of which have been isolated and partly characterised. The main neutral triterpenes are: dammadienone, $C_{30}H_{48}O$; dammadienol $C_{30}H_{50}O$; two isomeric hydroxydammarenones, $C_{30}H_{50}O_2$, and their related diols, $C_{30}H_{52}O_2$; and a third ketol, hydroxyhopanone, $C_{30}H_{50}O_2$. In addition to dammarolic acid, previously described, three further acids have been isolated one of which has been shown to be ursonic acid: the other two are dammarenolic acid, $C_{30}H_{50}O_3$, and dammarenonic acid, the latter obtained only in small yield as its methyl ester, $C_{31}H_{50}O_3$.

Dammar is the general name given to a group of natural resins originating from trees of the *Dipterocarpaceae* family which occur in Malaya, Indonesia, and the East Indies generally. The material in this investigation (obtained from Messrs. M. Hamburger and Sons Ltd., London) is described as "Pale Bold Indonesia Dammar." This variety is known also as "Dammar Mata Kuching" or "Cats Eye Dammar" and is said (Barry, "Natural Varnish Resins," London, 1932; Howes, "Vegetable Gums and Resins," Waltham, Mass., 1949) to originate from various species of *Hopea* notably *H. micrantha*, Hook. This material gives a paper chromatogram indistinguishable from that given by a sample of dammar from the Museum, Royal Botanic Gardens, Kew, bearing the label "Dammar Mata Kuching, from *Hopea* sp. Malaya, T. H. Barry 1932." It was moreover similarly indistinguishable (Mills and Werner, *J. Oil Colour Chemists' Assoc.*, 1954, **37**, 131) from Penak dammar, the second main variety of dammar, which originates from *Balanocarpus heimii*, King (Chengal tree), occurring mainly in Malaya. It seems therefore that dammars of different botanical origin are probably closely similar. For an account of the origin of the semi-fossil dammars such as Daging, Batu, Sengai, and Hitam see Barry (*op. cit.*). These resins contain higher proportions of polymerised material and oxidation products than the dammars of recent origin (Mills and Werner, *loc. cit.*).

References to early researches on dammar are given by Tschirch (Tschirch and Stock, "Die Harze," 3rd edn., Berlin, 1933, Vol. II, p. 395). The first systematic work was carried out by Tschirch and Glimann (*Arch. Pharm.*, 1896, 587). They isolated an acid which they named dammarolic acid. The neutral portion of the resin was divided into ethanol-soluble and ethanol-insoluble fractions, which were designated "α-" and "β-resene" respectively. From the "β-resene" Zinke and Unterkreuter (*Monatsh.*, 1918, **39**, 865) obtained a material $C_{30}H_{48}$. These results were confirmed by Parijs (*Pharm. Weekblad*, 1934, **71**, 354). Mladenović and Barković (*Monatsh.*, 1940, **73**, 206, 214) isolated an acid which they also called dammarolic acid though it differed from the material described by Tschirch. Barković and Vukčević-Kovačević (*Arhiv Kem.*, 1946, **18**, 66; *Chem. Abs.*, 1948, **42**, 2950) isolated two lactones from the products of the degradative oxidation of the neutral "α-resene" fraction; and Haas (*Pharm. Weekblad*, 1949, **84**, 505) obtained an acid which was almost certainly an impure sample of the dammarolic acid of Mladenović and Barković (*loc. cit.*). As will appear in the sequel dammar is a mixture of greater complexity than is suggested by the foregoing review.

The resin was first extracted with methanol and the methanol-soluble material chromatographed on alumina. Elution was carried out with the usual range of solvents, and fractions of equal volumes of eluant were examined by paper chromatography using a reversed-phase system devised for this purpose which employs odourless kerosene as the stationary phase and aqueous propan-2-ol as the mobile phase (Mills and Werner, *Nature*, 1952, **169**, 1064 and *loc. cit.*; cf. Rawlins and Werner, *Endeavour*, 1954, **51**, 140). The

fractions were then worked up by crystallisation or further chromatography according as they were apparently homogeneous or mixtures. The principal neutral constituents isolated are listed in Table 1.

TABLE 1. *Neutral constituents of dammar.*

	Approx. R_F	Formula	M. p.	$[\alpha]_D$
β-Resenes				
Ether-soluble	0·15	—	160—210°	−25°
Ether-insoluble	0·15	—	210—240	−33
Dammadienone	0·25	$(C_{30}H_{48}O)$	(72—75)	(+81)
Dammadienol	0·35	$C_{30}H_{50}O$	136—138	+47
Hydroxydammarenone I	0·62	$C_{30}H_{50}O_2$	145—147	+60
Hydroxydammarenone II	0·62	$C_{30}H_{50}O_2$	134—136	+66
Hydroxyhopanone	0·66	$C_{30}H_{50}O_2$	252—256	+64
Dammarenediol I	0·82	$C_{30}H_{52}O_2$	142—144	+27
Dammarenediol II	0·82	$C_{30}H_{52}O_2$	131—133	+33

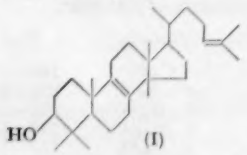
The " β-resene " has been re-examined by the methods of Zinke and Unterkreuter (*loc. cit.*), and similar materials were obtained. Both of these, however, contained oxygen, and determination of their molecular weights [by an isopiestic method (Wright, *Analyst*, 1948, **73**, 387) kindly carried out by Imperial Chemical Industries Limited, Paints Division, Slough] showed these to be higher than those corresponding to C_{30} compounds. Chromatography of the " β-resene " on alumina yielded no crystallisable material, but a continuous series of fractions of increasing molecular weight. It is concluded that the " β-resene " is a mixture of polymers of low molecular weight.

The alcohol dammadienol was isolated as its acetate by repeated crystallisation of a crude acetate which was itself apparently homogeneous on a paper chromatogram. The related ketone, dammadienone, was also obtained, with difficulty and in small yield, from an apparently homogeneous resinous fraction of the resin. Perbenzoic acid titration of dammadienol showed the presence of two double bonds and consequently if the empirical formulæ indicated are correct the compounds must be tetracyclic. The infrared spectra of the alcohol and ketone showed bands at 3075, 1640, and 890 cm.$^{-1}$, indicating the presence of a vinylidene group. Dammadienone gives a positive Zimmermann reaction and its infrared spectrum shows a band at 1711 cm.$^{-1}$ due to a six-membered ring ketone group. Barton and de Mayo (*J.*, 1954, 887) have shown that in the triterpene series this reaction is specific for compounds having a 3-oxo-group which must therefore be present in dammadienone. The method of molecular-rotation differences (Klyne, *J.*, 1954, 1979) indicates that the hydroxyl group of dammadienol has the more stable β-configuration ($\Delta_1 + 80°$).

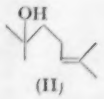
The two isomeric ketols, hydroxydammarenone I and II, were separated by chromatography and fractional crystallisation. On reduction with sodium and alcohol they yielded dammarenediol I and II which were also isolated directly from the resin. Perbenzoic acid titration indicated the presence of one double bond and consequently if the formulæ indicated are correct the compounds are tetracyclic. For reasons similar to those given above hydroxydammarenone I and II have a 3-oxo-group and dammarenediol I and II a 3β-hydroxy-group (diol I, $\Delta_1 + 31°$; diol II, $\Delta_1 + 24°$). The latter is further indicated by the mode of formation of the diols (Barton, *Experientia*, 1950, **6**, 316). Hydroxydammarenone I and II do not readily yield acetates but the presence of a hydroxyl group is shown by their infrared spectra (bands at 3620 cm.$^{-1}$).

Evidence for the tertiary nature of this hydroxyl group and of a tetracyclic formulation for these compounds was provided by their oxidation with chromium trioxide. In both cases acetone was obtained (as its 2 : 4-dinitrophenylhydrazone). Hydroxydammarenone I also yielded a crystalline compound, m. p. 218—220°, $C_{27}H_{42}O_3$, which gave no colour with tetranitromethane. Hydroxydammarenone II gave a similarly saturated compound, m. p. 183—185°, having the same formula. Both compounds had the same R_F value, gave similar colour reactions on the paper chromatogram, gave similar Zimmermann reactions, and had closely similar infrared spectra which showed bands at 1711 and 1785 cm.$^{-1}$ indicative of a six-membered ring ketone and a saturated γ-lactone grouping respectively.

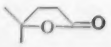
Both ketols must therefore contain an *iso*propylidene group. The hydroxyl group must be involved in the lactone formation and consequently, if a substituted side chain of lanosterol type, as in (I), is assumed, either ketol could have partial formula (II) and the two lactones partial formula (III).



(I)



(II)



(III)

The saturated nature of these two lactones and the comparatively low ultraviolet absorption of the hydroxydammarenone I and II in the 2100—2250-Å region indicate that there is no endocyclic tetrasubstituted double bond characteristic of tetracyclic triterpenes of the euphadienol and lanosterol series. Since all naturally occurring tetracyclic triterpenes of known structure contain this system, it was suggested by Professor D. H. R. Barton (personal communication) that these compounds might contain a *cyclo*propane ring as in *cyclo*artenol (Barton, *J.*, 1951, 1444). However, an attempted isomerisation of the keto-lactone I by treatment with hydrogen chloride in chloroform solution gave back starting material. It seems possible that the keto-lactone I may be identical with the lactone L_I, m. p. 216°, isolated by Barković and Vukčević-Kovačević (*loc. cit.*) on oxidation of dammar, despite the fact that they reported their compound as giving a yellow colour with tetranitromethane. Their analytical data agree almost as well with the formula $C_{27}H_{42}O_3$ as with their formula $C_{25}H_{40}O_3$.

A third ketol, hydroxyhopanone, is eluted from alumina together with hydroxydammarenone I and II from which, however, it is easily separated on account of its much lower solubility. For reasons similar to those given above this compound contains a 3-oxo-group and a tertiary or hindered secondary hydroxy-group. Though isomeric with the above ketols it differs from them in being saturated to tetranitromethane and must therefore be pentacyclic.

One further neutral compound, possibly not pure, was also isolated. This has been only cursorily examined and details are given in the Experimental section.

TABLE 2. *Acidic constituents of dammar.*

Acid	Approx. R_F	Formula	M. p.	$[\alpha]_D$
Dammarolic	0·96	$C_{30}H_{48-50}O_5$	315° *	+49°
Dammarenolic	0·86	$C_{30}H_{50}O_3$	138—142	+43
Ursonic	0·74	$C_{30}H_{46}O_3$	270—275 *	+80
Me dammarenonate	0·44	$C_{30}H_{50}O_3$	120—121·5	+62

* With decomp.

The acids were isolated principally by chromatography of the mixture of methyl esters, but ursonic acid was also obtained from the fractions of the main chromatographic separation lying between those containing dammadienone and dammadienol. It is highly unlikely that the acid itself could have been eluted at this stage, and it is believed to have been formed from a labile constituent which was detected on the paper chromatograms of these fractions but has not so far been isolated. Nevertheless the acid is believed to be an original constituent of dammar since it was also isolated from the ether–methanol fractions of the same separation where it might be expected to be eluted. Furthermore its methyl ester was obtained in the separation of the esters of the mixed acids. The melting point and rotation of the methyl ester were in good agreement with the recorded values for methyl ursonate and the melting point was undepressed on admixture with an authentic specimen (kindly supplied by Mr. K. H. Overton). This identification was confirmed by conversion of the ester into uvaol and methyl ursolate acetate.

The acid, m. p. *ca.* 315°, obtained in the present work from the ether-insoluble portion

of the acid fraction, appears to be identical with the dammarolic acid, m. p. 325°, of Mladenović and Barković (*loc. cit.*). The acetate and acetate methyl ester were prepared. Both had wide melting ranges and gave unsatisfactory analyses. The methyl ester, which was crystalline and of sharp melting point, gave a yellow colour with tetranitromethane, though Mladenović and Barković state that the acid is saturated.

Dammarenolic acid appears to be the major acidic constituent of the resin. It was isolated as its methyl ester. This did not yield an acetate but the presence of a hydroxyl group was shown by an infrared band at 3620 cm.$^{-1}$. Perbenzoic acid titration showed the presence of two double bonds, one of which is present in a vinylidene group (infrared spectrum: bands at 3070, 1640, and 895 cm.$^{-1}$). If the suggested molecular formulæ for the acid and its derivatives are correct a tricyclic formulation must be assumed for them. Oxidation of the ester yielded acetone and a trisnor-γ-lactone, which suggests the presence of a side chain similar to that in the hydroxydammarenones. Reduction of the ester with lithium aluminium hydride yielded a diol characterised as its monoacetate.

Methyl dammarenonate, the ester of an acid which has not itself been prepared, was also obtained by chromatography of the mixed esters. The ultraviolet absorption was characteristic of an αβ-unsaturated ester and the infrared spectrum showed a strong band at 1707 cm.$^{-1}$ due to six-membered ring ketone and conjugated ester groups. The ester gave a positive Zimmermann reaction.

Experimental

Rotations were determined in $CHCl_3$ at room temperature. Alumina used for chromatography was Peter Spence neutral type "H" partially deactivated by being spread out in the air overnight. Light petroleum refers to the fraction of boiling range 60—80°.

Paper Chromatography.—R_F values are liable to considerable variation and must be regarded as relative only. Those given were determined under comparable conditions on paper impregnated with odourless kerosene, the developing solvent being the lower phase of the system propan-2-ol–water–odourless kerosene (7 : 3 : 1 by vol.). In the Halphen–Hicks reaction (Hicks, *J. Ind. Eng. Chem.*, 1911, **3**, 86) the dried papers are sprayed with a solution of phenol in carbon tetrachloride and suspended in bromine vapour for a short while. Not all triterpenes give a positive reaction in this test and the modified Noller reaction (Noller *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 3047) is more general. In this the papers are suspended in a jar full of the vapour from a mixture of thionyl chloride with about 20% of stannic chloride. The colours produced are usually intensified and sometimes undergo characteristic changes if after ½ minute's exposure the strips are removed for about ½ min. and then replaced for a further short period. The reaction with antimony trichloride, described by Hashimoto (*Experientia*, 1953, **9**, 194), appears to be less sensitive than the above reactions.

β-*Resene.*—The coarsely ground resin (1 kg.) was digested with hot methanol (4 l.) until a uniform suspension was obtained. The cooled solution was filtered from the insoluble β-resene (*ca.* 290 g.) and the "dewaxed" dammar recovered by pouring the solution into a large volume of brine and filtering off the resin. The β-resene was purified by precipitation three times from chloroform (100 g. in 100 ml.) with methanol (400 ml.). It was divided into ether-soluble and ether-insoluble fractions by the methods of Zincke and Unterkreuter (*loc. cit.*). The ether-soluble material had m. p. 160—210°, $[\alpha]_D$ −25° (*c* 1·59) (Found: C, 85·7; H, 11·55%; *M*, 3220, 3200). The ether-insoluble material had m. p. 210—240°, $[\alpha]_D$ −33° (*c* 1·55) (Found: C, 85·4; H, 11·55%; *M*, 4700, 5120).

The β-resene mixture (5 g.) was absorbed from light petroleum on alumina (30 × 3·8 cm.), and elution with gradually increasing concentrations of benzene in light petroleum, followed by chloroform in benzene, and 38 100-ml. fractions were collected. Molecular weights increased with the number of the fraction, *e.g.*,

Number of fraction	3	13	18	23	37
Mol. wt.	1830	2500	2600	3000	4040

Main Chromatographic Separation.—"Dewaxed" dammar (120 g.) was warmed with light petroleum (200 ml.) until a uniform suspension was obtained which was then diluted to 1 l. with light petroleum. A sticky precipitate, comprising the bulk of the acidic constituents, was allowed to settle. The supernatant solution was run during ½ hr. on to alumina (85 × 4·8 cm.,

ca. 1300 g.), and washed in with several small volumes of light petroleum. The following eluting solvents were then passed : (i) benzene in light petroleum increasing in concentration by increments of 5% of benzene every 500 ml. of eluant from 0 to 50% of benzene and by increments of 10% of benzene every 500 ml. of eluant from 60 to 100% of benzene; (ii) ether in benzene increasing in concentration by increments of 10% of ether every 250 ml. of eluant from 10% to 100% of ether; (iii) methanol in ether increasing in concentration by increments of 10% of methanol every 250 ml. of eluant from 10% to 100% of methanol. Fractions of 250 ml. were collected, about 56 in all. Paper chromatograms of every other fraction were run, one drop (20 μl.) being used. The composition being thus disclosed the fractions were divided into batches showing maximum separation of constituents and evaporated, and the material worked up as follows :

Fractions 5—6. These contained residual β-resene (R_F 0·15) and some essential oil, and were not examined further.

Fractions 11—15 (*ca.* 3·5 g.) Although the resinous material from these fractions gave a single spot on the paper chromatogram it did not crystallise directly from the usual solvents (Found : C, 84·0; H, 11·35. Calc. for $C_{30}H_{48}O$: C, 84·85; H, 11·4%). It readily yielded, by the usual methods, a crystalline oxime mixture, m. p. 200—210° (from aqueous ethanol) (Found : C, 81·8; H, 11·35; N, 3·15. Calc. for $C_{30}H_{49}ON$: C, 81·95; H, 11·25; N, 3·2%), and a 2 : 4-dinitrophenylhydrazone mixture, m. p. 140—155° (Found : C, 71·35; H, 8·85; N, 9·45. Calc. for $C_{36}H_{52}O_4N_4$: C, 71·5; H, 8·65; N, 9·25%). The ketone mixture (2 g.) was absorbed from light petroleum (25 ml.) on alumina (20 × 1·8 cm.). Benzene–light petroleum (1 : 19) eluted the material in 5 100-ml. fractions. The first did not crystallise. The material from the second and third fraction was dissolved in hot ethanol, and the solution cooled to room temperature, decanted from gum, and set aside overnight. A small quantity of waxy solid which separated was treated as above with methanol, giving nodules which, on recrystallisation twice from methanol, gave leaflets (20 mg.), m. p. 72—75°, $[\alpha]_D$ +81° (*c* 0·78), R_F 0·25. Colour reactions : Noller, mauvish; Halphen–Hicks, orange pink. The compound gave a yellow colour with tetranitromethane and a positive Zimmermann reaction.

Fractions 16—23 (*ca.* 9 g.). These fractions, when examined shortly after running from the column, showed a single spot of R_F value 0·42 which gave a blue Noller reaction and no colour in the Halphen–Hicks test. It was not possible to isolate the material corresponding to this spot, since in a few days or possibly during working up the substance it is almost completely converted into ursonic acid, R_F 0·74, a substantial amount of which is present in the fractions after only one day. In one experiment the fractions were treated as follows :

After 4 days the solutions were evaporated and divided into acidic (*ca.* 7 g.) and neutral (*ca.* 2 g.) fractions by extraction with aqueous alkali. Rechromatography of the neutral fraction failed to yield crystalline material even though once again some of the fractions initially contained only the original substance of R_F 0·42. The acid fraction, crystallised from aqueous dioxan, gave impure ursonic acid (5 g.), m. p. 250—268° (decomp.). The material was dissolved in ethanol, a large volume being necessary owing to the presence of a poorly soluble neutral *compound* which separated from the dilute solution as prisms (350 mg.), m. p. *ca.* 300° (decomp. with prior sintering) (after recrystallisation from ethanol–ethyl acetate), $[\alpha]_D$ +66° (*c* 0·74) (Found : C, 76·5; H, 9·95. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). This was probably present in the aqueous alkaline extract, which was very cloudy, on account of its very low solubility in ether. It was unchanged on treatment with diazomethane, and gave no colour in the Halphen–Hicks or the Noller reaction or with tetranitromethane. It gave a positive Zimmermann reaction. The infrared spectrum determined in Nujol showed bands at 3500, 1733, and 1703 cm.$^{-1}$. Concentration of the ethanol solution gave ursonic acid, a portion of which, crystallised several times from methanol, had m. p. 270—275° (decomp.), $[\alpha]_D$ +80° (*c* 0·9) (Found : C, 78·95; H, 10·25. Calc. for $C_{30}H_{46}O_3$: C, 79·25; H, 10·2%), R_F 0·74. Colour reactions : Noller, pale orange, through mauve to bright blue; Halphen–Hicks, negative. The bulk of the acid was methylated with diazomethane and crystallised from ethanol, to give methyl ursonate as large plates, m. p. and mixed m. p. 192—194°, $[\alpha]_D$ +84° (*c*, 1·23) (Found : C, 79·1; H, 10·45. Calc. for $C_{31}H_{48}O_3$: C, 79·45; H, 10·3%), R_F 0·46. Colour reactions : Noller, pale orange turning to mauve (slow, long exposure necessary); Halphen–Hicks, negative. Reduction of the ester with lithium aluminium hydride, followed by chromatography and crystallisatiom from methanol, yielded uvaol, as long needles, m. p. 225—227°, $[\alpha]_D$ +63° (*c*, 1·34) (Found : C, 81·4; H, 11·35. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%), R_F 0·8. Colour reactions : Noller, mauve; Halphen–Hicks, negative. Reduction of the ester with sodium borohydride, acetylation of the product with pyridine–acetic anhydride, chromatography,

and crystallisation from methanol yielded methyl ursolate acetate, m. p. and mixed m. p. 245—247°, $[\alpha]_D$ +55° (*c* 1·22) (Found: C, 77·35; H, 10·4. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·25%), R_F 0·33. Colour reactions: Noller, pink; Halphen–Hicks, weak blue.

Fractions 25—34 (*ca.* 12 g.). These fractions consist largely of a mixture of alcohols (R_F 0·35) and ketols (R_F 0·62). Two other spots are also present on the paper chromatogram but the materials they represent have not been isolated. The material was treated with pyridine–acetic anhydride overnight and the products, isolated in the usual way, were chromatographed on alumina (30 × 3·8 cm.). Light petroleum eluted the alcohol acetate mixture (R_F 0·19), and the unchanged ketols were subsequently eluted by gradually increasing concentrations of benzene in light petroleum. The acetate mixture, crystallised from aqueous ethanol, had m. p. 100—130° (4·5 g.). It was rechromatographed on alumina. The earlier material eluted, which carried with it a small amount of β-resene, was rejected, and the remaining material was crystallised many times from ethanol to yield *dammadienyl acetate* as flat needles (300 mg.), m. p. 151—153°, $[\alpha]_D$ +60° (*c* 0·68) (Found: C, 81·95; H, 11·35. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%), R_F 0·19. Colour reactions: Noller, ill-defined greyish-mauve; Halphen–Hicks, orange–brown ⟶ pink. The material gave a yellow colour with tetranitromethane. Hydrolysis of dammadienyl acetate for 6 hr. with 10% ethanolic potassium hydroxide followed by chromatographic purification and crystallisation from methanol yielded *dammadienol* as needles, m. p. 136—138°, $[\alpha]_D$ +47° (*c* 0·6) (Found: C, 84·3; H, 11·9. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%), R_F 0·35. Colour reactions were as for the acetate. The infrared spectrum, determined in CS_2, showed bands at 3620, 3070, 1640, and 895 cm.$^{-1}$.

The ketol fractions were combined and crystallised from light petroleum. This is desirable as it removes any β-resene, which tends to be present in all the fractions in small quantities and is not removed by crystallisation from polar solvents such as methanol.

The ketol mixture (m. p. 110—130°) was dissolved in methanol and allowed to crystallise overnight. On white nodular material clusters of large plates rested. These were picked out and had m. p. 128—133°. Upon recrystallisation three times from methanol they gave *hydroxydammarenone II* as plates (300 mg.), m. p. 134—136°, $[\alpha]_D$ +66° (*c* 1·18) (Found: C, 81·55; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%), R_F 0·63. Colour reactions: Noller, greenish; Halphen–Hicks, orange–brown ⟶ pink. The material gave a yellow colour with tetranitromethane and a positive Zimmermann reaction. The infrared spectrum in CS_2 showed bands at 3620 and 1711 cm.$^{-1}$. Light absorption in EtOH at 210, 215, 220, and 225 mμ had ε 1670, 660, 185, and 45 respectively; $\lambda_{max.}$ 290 mμ (ε 36). The remaining nodular material and a further quantity recovered from the mother-liquor (total 4 g.) were adsorbed from light petroleum on alumina (30 × 3·8 cm.), and eluted with increasing concentrations of benzene in light petroleum (30 × 100 ml.). The eluted materials crystallised from aqueous methanol. The first two fractions yielded hydroxydammarenone II, m. p. 127—132°, raised to the m. p. of the above material by crystallisation. The remaining fractions yielded mixtures, m. p. 118—125°, which were combined and wastefully crystallised six times from methanol, to yield *hydroxydammarenone I* as needles (300 mg.), m. p. 145—147° (depressed to 120—130° on admixture with hydroxydammarenone II), $[\alpha]_D$ +60° (*c* 1·34) (Found: C, 81·25; H, 11·5%), R_F and colour reaction as for hydroxydammarenone II. The infrared spectrum in CS_2 also showed bands at 3620 and 1711 cm.$^{-1}$ and was almost identical with that of hydroxydammarenone II.

Fractions 35—41 (13 g.). The material was dissolved in ether (100 ml.) and set aside overnight. *Hydroxyhopanone* separated as fine needles (500 mg.), m. p. 246—250°, raised by several crystallisations from ethanol to 252—256° (slight charring), $[\alpha]_D$ +64° (*c* 1·68) (Found: C, 81·35; H, 11·55. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%), R_F 0·66. (When run alone on a paper chromatogram this material tends to crystallise at the origin, causing streaking.) Colour reactions: Noller, brownish; Halphen–Hicks, brownish-yellow. The material showed no colour with tetranitromethane, and gave a positive Zimmermann reaction. The infrared spectrum in CS_2 showed bands at 3610 and 1706 cm.$^{-1}$.

On treatment with pyridine–acetic anhydride overnight at room temperature this compound was recovered unchanged (m. p., mixed m. p., R_F). Treatment with cold ethanolic 2 : 4-dinitrophenylhydrazine sulphate containing an excess of sulphuric acid yielded the 2 : 4-*dinitrophenylhydrazone* of the dehydration product (or products), m. p. 241—243° (decomp.) (after chromatographic purification and crystallisation from ethanol–benzene) (Found: C, 71·2; H, 8·85. $C_{36}H_{52}O_4N_4$ requires C, 71·5; H, 8·65%). The *oxime*, crystallised from ethanol–chloroform, had m. p. 295—298° (decomp.) (Found: C, 78·25; H, 11·35; N, 3·2. $C_{30}H_{51}O_2N$ requires C, 78·7; 11·25; N, 3·05%).

The material remaining in the ether solution from the above crystallisation consisted largely

of a mixture of hydroxydammarenone I and II which after further chromatographic purification and five wasteful crystallisations from methanol yielded hydroxydammarenone I (800 mg.).

Fractions **43—46** (5 g.). The material from these fractions was adsorbed from benzene on alumina (25 × 3·8 cm.). Elution was first with benzene and then with 5 and 10% of ether in benzene (20 × 100 ml.). The fractions 2—7 gave material which on crystallisation twice from aqueous methanol and several times from nitromethane gave *dammarenediol II* as needles (500 mg.), m. p. 131—133°, $[\alpha]_D$ +33° (*c* 1·19) (Found: C, 81·0; H, 11·9. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). The *monoacetate* was prepared by pyridine–acetic anhydride overnight and after chromatography and crystallisation from methanol was obtained as plates, m. p. 135—137°, $[\alpha]_D$ +37° (*c* 0·92) (Found: C, 79·2; H, 11·5. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%). The material from fractions 10—20, recrystallised from aqueous methanol and from nitromethane, gave *dammarenediol I* as needles (400 mg.), m. p. 142—144°, $[\alpha]_D$ +27° (*c* 1·23) (Found: C, 80·6; H, 11·9%). The *monoacetate*, prepared and purified as described above, was obtained as needles, m. p. 149—150° (clearing 151°), $[\alpha]_D$ +32° (*c* 0·87) (Found: C, 79·0; H, 11·3%). The R_F of both diols was 0·82. Colour reactions: Halphen–Hicks, orange-pink; Noller, mauvish-grey. The acetates had R_F 0·5 and gave similar colour reactions.

Fractions **51** *and* **52** (2 g.). These fractions showed on a paper chromatogram a spot having the same R_F and giving the same colour reactions as ursonic acid. The material was divided into acidic and neutral fractions. The acidic fraction was esterified with diazomethane, and the product adsorbed from benzene on alumina (20 × 1·8 cm.). Elution with the same solvent yielded an ester which, crystallised several times from methanol, gave in small yield methyl ursonate as stout needles (100 mg.), m. p. and mixed m. p. 192—195°, $[\alpha]_D$ +86° (*c* 0·5). The neutral fraction was not investigated.

Isolation of Further Acids.—The light petroleum-insoluble portion of the resin was dissolved in ether and extracted with 5% aqueous potassium hydroxide, then several times with water. The aqueous extracts were made just acid by 2N-hydrochloric acid; the precipitated acids were washed with water, dried (SiO_2 gel), and refluxed with ether (10 g. in 100 ml.). On cooling, the solution deposited a small amount of insoluble material which was recovered by filtration or centrifuging. This material, dissolved in ethanol, was decolorised with charcoal, and after crystallising several times from acetone yielded dammarolic acid as a microcrystalline powder, m. p. 315° (decomp.; sintering slightly at 250° and charring at 280°), $[\alpha]_D$ +49° (*c* 1·58) (Found: C, 71·3; H, 10·0. Calc. for $C_{30}H_{48}O_6$: C, 71·4; H, 9·6. Calc. for $C_{30}H_{50}O_6$: C, 71·1; H, 9·95%), R_F 0·96. Colour reactions: Noller, pale orange ⟶ mauve ⟶ blue; Halphen–Hicks, negative. The material gave a very pale yellow colour with tetranitromethane. The methyl ester (diazomethane) formed needles, m. p. 222—224°, $[\alpha]_D$ +52° (*c* 1·24), from methanol (Found: C, 72·4; H, 10·0. Calc. for $C_{31}H_{50}O_6$: C, 71·8; H, 9·7. Calc. for $C_{31}H_{52}O_6$: C, 71·5; H, 10·05%. The figures given are the least unsatisfactory of several analyses). The acetate, prepared in the usual way, had m. p. 160—175°, $[\alpha]_D$ +37° (*c* 1·19) (Found: C, 70·5; H, 9·15%). The *acetate methyl ester* had m. p. 145—150° (from methanol). The m. p. was lowered to 125—140° on drying at 100° for a short while (Found: C, 71·35; H, 9·6%).

The acids remaining in the ether solution were methylated with diazomethane, and the resulting resinous mixture of esters (20 g.) was absorbed from light petroleum on alumina (30 × 3·8 cm.), and elution was carried out with light petroleum (1·5 l.), followed by benzene in light petroleum increasing in concentration by increments of 5% of benzene every 100 ml. of eluate up to 50% of benzene and by increments of 10% of benzene from 60 to 100% of benzene. Fractions of 100 ml. were collected and their composition determined by paper chromatography.

The column was rather overloaded and fractions 4 and 5 contained an unresolved mixture which was therefore re-chromatographed as described below.

Fractions 10—25, individually crystallised from aqueous methanol, yielded similar materials (total 2·5 g.), m. p. 86—90° which, combined and recrystallised from aqueous methanol and methanol, yielded *methyl dammarenolate* as needles, m. p. 89—92° not raised by further crystallisation, $[\alpha]_D$ +41° (*c* 1·45) (Found: C, 78·7; H, 11·25. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%), R_F 0·54. Colour reactions: Noller, pale orange ⟶ greyish-mauve; Halphen–Hicks, orange-brown ⟶ pink. The material gave a yellow colour with tetranitromethane. The infrared spectrum in CS_2 showed bands at 3620, 1746, 3070, 1640, 895 cm.$^{-1}$. Treating the ester with pyridine–acetic anhydride overnight at 20° or for 40 min. on the steam-bath gave only starting material (m. p., mixed m. p., R_F). Hydrolysis of the ester for 48 hr. at 20° with 10% ethanolic potassium hydroxide yielded *dammarenolic acid*, needles, m. p. 138—142° (from aqueous methanol), $[\alpha]_D$ +43° (*c* 0·98) (Found: C, 78·45; H, 11·15. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%), R_F 0·86. Colour reactions as for the methyl ester.

The material from fractions 4 and 5 was re-adsorbed from light petroleum on alumina (25 × 3·8 cm.). Elution with increasing concentrations of benzene in light petroleum as above and crystallisation from methanol yielded, in order of elution: (*a*) ***Methyl dammarenonate***, long needles, m. p. 120—121·5° (from methanol) (70 mg.), $[\alpha]_D$ +62° (*c* 0·78) (Found: C, 78·75; H, 10·45. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%), R_F 0·44. Colour reactions: Noller, yellow ⟶ brownish; Halphen–Hicks, yellow-brown. The material gave a yellow colour with tetranitromethane and a positive Zimmermann reaction. The infrared spectrum in CS_2 showed a broad and intense band at 1707 cm.$^{-1}$. Light absorption in ethanol: $\lambda_{max.}$ 214 mμ (ε 16,000). (*b*) Methyl ursonate, rectangular plates, m. p. and mixed m. p. 191—194° (from ethanol) (200 mg.), $[\alpha]_D$ +85° (*c* 1·03) (Found: C, 79·25; H, 10·4%). (*c*) A further 1 g. of methyl dammarenolate, m. p. 86—90° raised by further crystallisation to the m. p. of the material previously described.

Oxidation of Dammadienol.—The alcohol (150 mg.) in benzene (1 ml.) and "AnalaR" acetic acid (5 ml.) was treated with chromium trioxide (100 mg.) in a few drops of water, and set aside overnight. The products were isolated in the usual way. The acid fraction (40 mg.) showed on a paper chromatogram a single spot of high R_F, and colour reactions: Noller, mauve; Halphen–Hicks, negative. It was not examined further. The neutral fraction was adsorbed from light petroleum on alumina (10 × 1·2 cm.). Benzene–light petroleum (1 : 19) eluted a product which, crystallised twice from methanol, gave *dammadienone* as leaflets (45 mg.), m. p. 79—80°, mixed m. p. with the material (m. p. 72—75°) isolated direct from the resin 72—76°, $[\alpha]_D$ +90° (*c* 0·56) (Found: C, 84·55; H, 11·55. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%). The R_F and colour reactions were identical with those of the material (m. p. 72—75°) isolated from the resin. The infrared spectrum in CS_2 showed bands at 1711, 3070, 1640, and 895 cm.$^{-1}$.

Oxidation of Hydroxydammarenone I.—The ketol I (0·5 g.) in benzene (2·5 ml.) and "AnalaR" acetic acid (15 ml.) was treated with chromium trioxide (0·4 g.) in a few drops of water, and set aside overnight at 20°. The solution was poured into dilute aqueous sodium metabisulphite and steam-distilled. To the distillate (50 ml.) was added a solution of 2 : 4-dinitrophenylhydrazine (250 mg.) in dilute hydrochloric acid. The mixture was extracted with benzene and the product adsorbed from benzene on alumina (20 × 1·8 cm.). Benzene detached and eluted a band, which on evaporation and crystallisation from methanol gave acetone 2 : 4-dinitrophenylhydrazone (130 mg.), m. p. and mixed m. p. 125—127°. A blank experiment, identical with the above apart from the omission of the hydroxydammarenone I, yielded no acetone 2 : 4-dinitrophenylhydrazone. The residue from the steam-distillation was worked up in the usual way and adsorbed from benzene on alumina (20 × 1·8 cm.). Benzene–ether (9 : 1; 250 ml.) eluted a product, *keto-lactone I*, which crystallised from methanol as needles (260 mg.), m. p. 211—217°, raised by several further crystallisations to 218—220°, $[\alpha]_D$ +53° (*c* 1·11) (Found: C, 77·8, 78·05; H, 10·25, 10·2. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%), R_F 0·9. Colour reactions: Noller, yellow ⟶ mauve; Halphen–Hicks, negative. The compound gave no colour with tetranitromethane and a positive Zimmermann reaction. The infrared spectrum in CS_2 showed bands at 1711 and 1785 cm.$^{-1}$.

Oxidation of Dammarenediol II.—Dammarenediol II (300 mg.) in benzene (1·5 ml.) and "AnalaR" acetic acid (10 ml.) was treated with chromium trioxide (400 mg.) in a few drops of water and set aside overnight at 20°. The procedure was then as in the preceding section, acetone 2 : 4-dinitrophenylhydrazone (60 mg.) being obtained, having m. p. and mixed m. p. 125—127°. The residue from the steam-distillation was worked up in the usual way and adsorbed from benzene on alumina (15 × 1·8 cm.). Benzene–ether (9 : 1; 200 ml.) eluted a product, *keto-lactone II*, which crystallised from aqueous methanol as platelets (150 mg.), m. p. 178—182° raised by crystallisation from methanol to m. p. 183—185° $[\alpha]_D$ +69° (*c* 1·06) (Found: C, 77·7; H, 10·45. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%). The R_F, Noller, and Halphen–Hicks colours, and the tetranitromethane and Zimmermann reactions were as for the keto-lactone I. The infrared spectrum in CS_2 showed bands at 1711 and 1785 cm.$^{-1}$.

Oxidation of Hydroxydammarenone II.—The ketol II (200 mg.) in benzene (1 ml.) and "AnalaR" acetic acid (7·5 ml.) was treated with chromium tricxide (150 mg.) and the solution kept overnight. The product was isolated, chromatographed, and crystallised as in the preceding section, to yield the keto-lactone II, m. p. and mixed m. p. 183—185°.

Oxidation of Methyl Dammarenolate.—Methyl dammarenolate (500 mg.) in benzene (2·5 ml.) and "AnalaR" acetic acid (15 ml.) was treated with chromium trioxide (400 mg.) in a few drops of water, and the solution kept overnight at 20°. The procedure was as in the oxidation of hydroxydammarenone I, acetone 2 : 4-dinitrophenylhydrazone (110 mg.) being obtained (m. p.

and mixed m. p. 126—128°). The residue from the steam-distillation was adsorbed from benzene–light petroleum (1 : 1) on alumina (20 × 1·8 cm.). Elution with the same solvent (750 ml.) yielded a few mg. of material which crystallised from aqueous methanol as needles, m. p. 114—120°, R_F 0·45. This material was not further examined. Elution with benzene (500 ml.) yielded the main product, a *methyl ester lactone*, which crystallised from aqueous methanol as needles, m. p. 121—126°, raised to m. p. 125—128° by further crystallisation from methanol, $[\alpha]_D$ +43° (*c* 0·7) (Found: C, 75·85; H, 10·15. $C_{28}H_{44}O_4$ requires C, 75·65; H, 10·0%), R_F 0·93. Colour reactions: Noller, pink or mauve; Halphen–Hicks, negative. The compound gave a pale yellow colour with tetranitromethane and a negative Zimmermann reaction. The infrared spectrum in CS_2 showed bands at 1785, 1746, 3060, 1638, and 895 cm.$^{-1}$.

Reduction of Hydroxydammarenone I.—The ketol I (150 mg.) was dissolved in ethanol (35 ml.) and sodium (3 g.) added during ½ hr. The product was isolated in the usual way and adsorbed from benzene on alumina (10 × 1·8 cm.). Benzene–ether (19 : 1; 500 ml.) eluted a product which was crystallised from aqueous methanol and then from nitromethane to give *dammarenediol I* as needles (110 mg.), m. p. 142—144°, undepressed on admixture with the sample isolated from the resin, $[\alpha]_D$ +27° (*c* 1·16). The R_F and colour reactions were also identical.

Reduction of Hydroxydammarenone II.—The ketol II (200 mg.) was reduced in ethanol (50 ml.) with sodium (4 g.), and the product isolated and chromatographed as above. Crystallisation from aqueous methanol and then from nitromethane yielded *dammarenediol II* (150 mg)., m. p. 130—132° (undepressed on admixture with the sample isolated from the resin), $[\alpha]_D$ +34° (*c* 1·09).

Attempted Isomerisation of Keto-lactone I.—A stream of dry hydrogen chloride was passed for 3 hr. through a solution of the keto-lactone I (70 mg.) in chloroform (20 ml.). The solvent was removed *in vacuo*. The residue, crystallised from methanol, gave unchanged material (50 mg.), m. p. and mixed m. p. 215—218°.

Lithium Aluminium Hydride Reduction of Methyl Dammarenolate.—Methyl dammarenolate (250 mg.) was refluxed for 3 hr. with lithium aluminium hydride (150 mg.) in dry ether (50 ml.). Water and 2N-sulphuric acid were added and the product was isolated with ether. The material did not crystallise readily and was therefore acetylated overnight with pyridine–acetic anhydride; the product, chromatographed over alumina in benzene and crystallised from methanol, was a *diol monoacetate*, needles (200 mg.), m. p. 124—127°, $[\alpha]_D$ +45° (*c* 0·97) (Found: 78·85; H, 11·3. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%), R_F 0·55. Colour reactions: Noller, mauvish; Halphen–Hicks, orange-brown to pink.

Perbenzoic Acid Titrations.—Titration in chloroform at 0° gave the results tabulated.

	Acid added (mols.)	Acid consumed (mols.)		
		1 day	2 days	4 days
Dammadienol	5·1	2·13	2·28	2·31
Dammarenediol II monoacetate	4·4	1·07	1·05	1·05
Me dammarenolate	4·4	1·93	2·05	2·03
Me ursonate	4·1	0·05	—	0·0

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The Electrical Conductivity of Dinitrogen Tetroxide Solutions in Sulphuric, Selenic, and Phosphoric Acids.

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The conductivities of solutions of dinitrogen tetroxide in sulphuric acid have been measured at concentrations previously unexplored. The conductivity reaches a fairly sharp maximum at a concentration of 6 mol. % and, thereafter, falls regularly to about one-fifth of that value at approximately 48 mol. %. Here nitrosyl hydrogen sulphate, $NOHSO_4$, is formed, followed, at a slightly higher concentration, by the separation of dinitrogen tetroxide as an immiscible layer.

Dinitrogen tetroxide in selenic and phosphoric acids gives similar conductivity–concentration curves, except that their maxima appear at a much lower concentration. Furthermore, the conductivities at the limit of homogeneity are well below that of the solvent. At a sufficient concentration, nitrosyl hydrogen selenate, $NOHSeO_4$, separates from selenic acid, but no solid is formed with phosphoric acid.

The significance of these facts is discussed in the light of viscosity and density measurements made in connection with this work, and the cryoscopic, Raman, and other examinations which have been made of parts of the dinitrogen tetroxide–sulphuric acid system by earlier investigators.

So far as we know the electrical conductivities of solutions of dinitrogen tetroxide in anhydrous sulphuric acid have not been measured beyond a concentration of 0·663 mol. % (Gillespie and Wasif, *J.*, 1953, 209), although homogeneous solutions of 45 mol. % are easily prepared. Nothing has been found in the literature about its solutions in selenic and phosphoric acids; there is but one mention of the conductivity of anhydrous phosphoric (Mason and Culvern, *J. Amer. Chem. Soc.*, 1949, **71**, 2387), and none of anhydrous selenic acid. Yet both dissolve the oxide in considerable proportions: selenic acid about 40 mol. %, and phosphoric acid about 10 mol. %. This paper provides the missing conductivities, and also some information on the densities and viscosities of the solutions in sulphuric acid. These data are discussed in relation to conclusions reached by other workers, from physicochemical studies on certain parts of the dinitrogen tetroxide–sulphuric acid system.

As dinitrogen tetroxide is added to the acids at room temperature, they change, at a concentration characteristic of each, from colourless to yellow. The yellow solutions become colourless on cooling; this suggests the colour is due, in part at least, to the presence of molecular dinitrogen tetroxide. With a further increase in concentration the yellow becomes darker, and, eventually, separation into two layers takes place; the less dense one is liquid dinitrogen tetroxide which, incidentally, we find to be completely free from the acid in question. It did, however, contain nitric acid which was not present in the original liquid. Somewhat below the concentrations at which the systems display immiscibility, colourless crystals of nitrosyl hydrogen sulphate and nitrosyl hydrogen selenate are formed in the respective solutions. Precipitation does not occur with phosphoric acid, nor can it be induced by cooling.

The relation we have found between conductivity and concentration in the three solutions is shown in Fig. 1. The three curves are similar: each rises to a fairly sharp maximum and then falls in an almost linear fashion. There are, however, real differences too: the solution in sulphuric acid does not reach the highest conductivity until 6·8 mol. % of tetroxide is present, and the lowest conductivity does not drop to that of sulphuric acid itself, whereas the solutions in selenic and phosphoric acids attain their peaks with very little tetroxide and their lowest conductivities are far below those of the respective acids. A reservation (see p. 3145) is necessary regarding our conductivity of selenic acid; by analogy with sulphuric acid, it might be lower. Associated with every maximum is a change from colourless to yellow.

About the solutions in sulphuric acid, especially the dilute solutions, there is a considerable background of knowledge. From crysocopic measurements on solutions up to a concentration of 0·45 mol. % (*i.e.*, far below that giving peak conductivity), Gillespie, Graham, Hughes, Ingold, and Peeling (*J.*, 1950, 2504) conclude that the tetroxide ionises thus

$$N_2O_4 + 3H_2SO_4 = NO^+ + NO_2^+ + H_3O^+ + 3HSO_4^-$$

Gillespie and Wasif (*J.*, 1953, 221) gave electrical conductivities of the liquids up to a concentration of 0·663 mol. % and found values—with which ours closely agree—greater than for a di(hydrogen sulphate), *e.g.*,

$$HNO_3 + 2H_2SO_4 = NO_2^+ + H_3O^+ + 2HSO_4^-$$

and approximately three times that for a mono(hydrogen sulphate), *e.g.*,

$$H_2O + H_2SO_4 = H_3O^+ + HSO_4^-,$$

thus substantiating deductions from cryoscopic evidence.

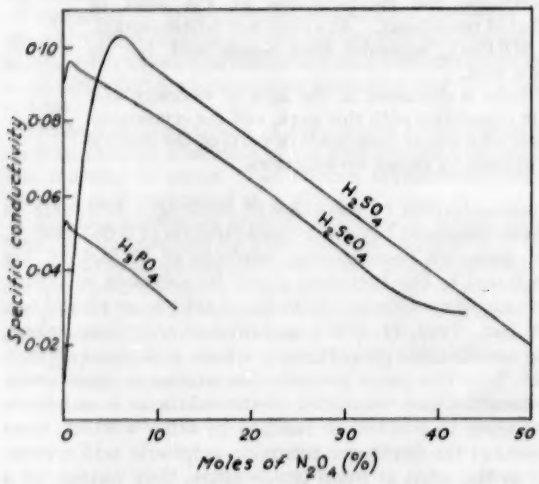


FIG. 1. *Specific electrical conductivities (ohms^{-1} cm.$^{-1}$) of solutions of dinitrogen tetroxide in sulphuric, selenic, and phosphoric acids.*

From the Raman spectrum of a solution of 10 mol. % Millen (*J.*, 1950, 2600) infers the presence of sulphuric acid, and the nitronium, nitrosonium, and hydrogen sulphate ions. This concentration is somewhat beyond that corresponding to our maximum conductivity. At 20 mol. %, well beyond the maximum conductivity, Millen observed "an increase in intensity, relative to the molecular sulphuric acid lines of the characteristic lines of the hydrogen sulphate ion, the nitronium ion and the nitrosonium ion," and also the frequencies 680, 1313, and 1670 cm.$^{-1}$. These he attributed to "a spectroscopically detectable quantity of molecular nitric acid formed according to the equation

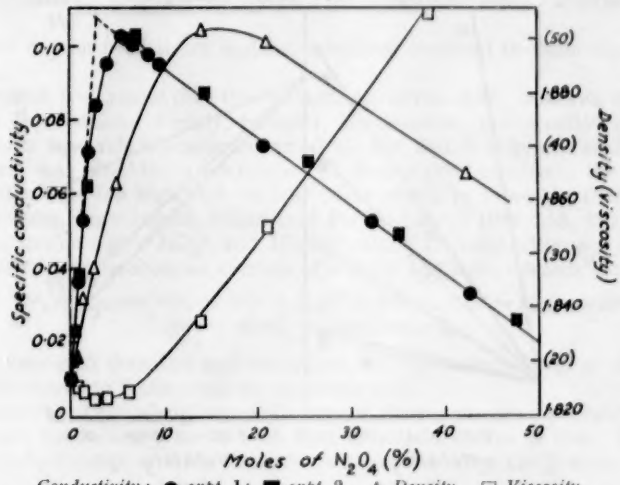
$$NO_2^+ + 2HSO_4^- + H_3O^+ = HNO_3 + 2H_2SO_4"$$

Since the Raman spectrum is not a very sensitive means of detecting nitric acid, it must have been there in appreciable quantity. Indeed, we found it in the dinitrogen tetroxide layer. This means that the above equilibrium showing the formation of nitric acid, which for dilute solutions lies almost completely to the left, for high concentrations is appreciably reversed. Probably the reversal begins before the yellow colour becomes visible: we imagine, at the concentration where the upward slope of the conductivity curve (Fig. 2) obviously lessens. Below this concentration the dinitrogen tetroxide is completely ionised (cf. Gillespie *et al.* and Gillespie and Wasif, *locc. cit.*), whereas, at the maximum conductivity, about half is un-ionised and beyond that point an increasing proportion remains in the molecular state. Eventually, it separates as a distinct phase.

But Millen's findings show the ionic concentration increases with that of dinitrogen tetroxide, at least up to 20 mol. % of the latter, despite the withdrawal of ions to form sulphuric and nitric acid molecules. Yet the electrical conductivity, due in great part to the hydrogen sulphate ion, HSO_4^-, falls after the concentration of 6·8 mol. % has been passed. In seeking to account for this anomaly, let us consider in turn density and viscosity.

The density of the sulphuric acid solutions (Fig. 2) increases by about 3·8%, being at a maximum with about 16 mol. % of dinitrogen tetroxide, and thence falling regularly. Increase in density suggests molecular association. Such an increase also occurs in dilute solutions of nitric acid in sulphuric acid (Gillespie and Wasif, *J.*, 1953, 215) and can be safely predicted for dinitrogen pentoxide and trioxide. Similar increases are found in solutions of the hydrogen sulphates of ammonium, lithium, sodium, potassium, and barium. Among the plots of density (Fig. 3; from data in Gillespie and Wasif, *ibid.*, p. 217, Figs.

FIG 2. *Specific electrical conductivity (ohms^{-1} cm.$^{-1}$), density, and relative viscosity of solutions of dinitrogen tetroxide in sulphuric acid.*



Conductivity: ● *expt.* 1; ■ *expt.* 2. △ *Density.* □ *Viscosity.*

1 and 4) ours for dinitrogen tetroxide lies close to theirs for nitric acid and above all the rest except barium; here the considerable solvation and possibly the mass of the cation are significant. It is noteworthy that they are greatly above that of water (Gillespie and Wasif, *J.*, 1953, 204) which is ionised according to the equation

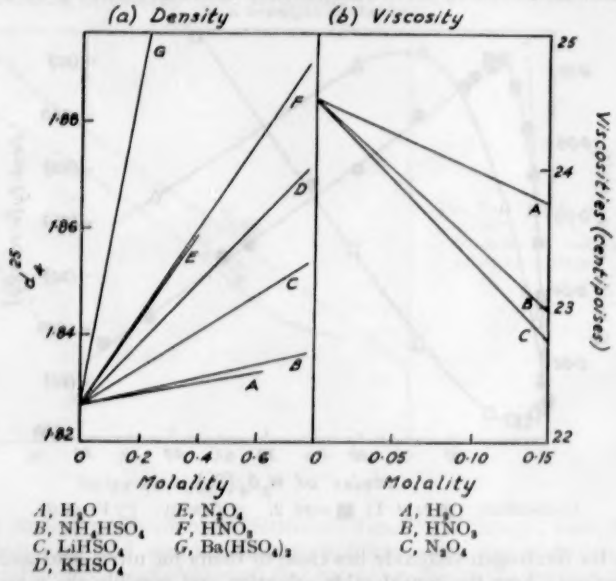
$$H_2O + H_2SO_4 \longrightarrow H_3O^+ + HSO_4^-$$

and that thus neither the HSO_4^- ion, solvated or otherwise, nor the hydroxonium ion can be responsible for the density changes observed. It is therefore necessary to turn to the other entities present: NO_2^+, NO^+, N_2O_4, and, at higher concentrations (20 mol. %), HNO_3. The metal cations are solvated in sulphuric acid; and, though evidence about the molal volume of the nitronium ion does not permit an estimate of the extent, there is good reason to suppose that it is solvated (Gillespie and Wasif, *loc. cit.*), the nitrosonium ion also. This leads us to believe that the rise of the density curve springs from a progressive increase in the number of solvated NO_2^+ and NO^+ ions. Millen's Raman results (*loc. cit.*) indicate that, at about 20 mol. %, equilibrium conditions involve the union of some ions to form nitric acid; and it is not improbable that nitrosyl hydrogen sulphate may be produced in the solution. The maximum of the density curve may very well correspond to the concentration of dinitrogen tetroxide at which the various equilibria lead to the maximum number of solvated NO_2^+ and NO^+ ions. If this be so, then the

regular fall of the curve from the maximum with increasing concentration can be regarded as a dilution effect due to molecular dinitrogen tetroxide. Similar behaviour has been observed by Gillespie and Wasif (*loc. cit.*) in solutions of sulphuryl chloride, which does not ionise in sulphuric acid. The curves of conductivity and density show so little parallelism, and the maximum of the latter is displaced so far in the direction of higher concentration, as to make it doubtful whether density and conductivity are intimately connected.

Very closely related to the conductivity curve, however, is that of the viscosity (Fig. 2). The viscosities of dilute solutions of water and nitric acid in sulphuric acid (Gillespie and Wasif, *loc. cit.*) fall with increasing concentration, the latter to much the same extent as we have found for dinitrogen tetroxide (Fig. 3). Our plot of viscosity, however, being carried further, shows a minimum at 2·6 mol. %. This is the concentration at which the initial slope of the conductivity curve when produced meets a continuation of the average

FIG. 3. *Densities and viscosities of certain dilute solutions in sulphuric acid.*



A, H_2O
B, NH_4HSO_4
C, $LiHSO_4$
D, $KHSO_4$
E, N_2O_4
F, HNO_3
G, $Ba(HSO_4)_2$

A, H_2O
B, HNO_3
C, N_2O_4

slope beyond the peak. It may well represent the concentration up to which all the dinitrogen tetroxide present is ionised and, of course, the point beyond which some is in the molecular form. Solvation has been invoked to explain the change in density; it cannot be used to account for the changes in viscosity. The solvation of metal cations has been given (Gillespie and Wasif, *loc. cit.*) as the cause of the increase in viscosity with concentration, but the argument clearly does not apply to NO_2^+ and NO^+. With these there is first a small fall in viscosity followed by a considerable regular rise. The rise we ascribe to compound formation, since compound formation of one kind or another is possible from about 2·6 mol. % and is progressively more probable up to the final concentration, *viz.*, the point where nitrosyl hydrogen sulphate crystallises. The electrical conductivity curve so closely follows the inverse of the viscosity curve as strongly to suggest that the viscous interference with the translation and rotation of the HSO_4^- ions largely accounts for the observed fall in conductivity. The dilution of the medium by un-ionised dinitrogen tetroxide must also reduce the conductivity, but, we think, not comparably with the change in viscosity.

Our views are set out schematically as four stages, corresponding to four regions of concentration in the dinitrogen tetroxide–sulphuric acid system.

Stage I (up to 2·6 mol. % and minimum viscosity). All the N_2O_4 is ionised :

$$N_2O_4 + 3H_2SO_4 \longrightarrow NO^+ + NO_2^+ + H_3O^+ + 3HSO_4^-$$

Stage II (from 2·6 to 6·8 mol. % and maximum conductivity). Some at least of the N_2O_4 is in the molecular condition. Compound formation begins and viscosity increases.

Stage III (6·8 to 16 mol. % and maximum density). Viscosity continues to increase. Solvated NO_2^+ and NO^+ ions reach maximum concentration in accordance with following equilibria :

(*a*) Nitric acid formed,

$$N_2O_4 + 3H_2SO_4 \rightleftharpoons NO^+ + NO_2^+ + H_3O^+ + 3HSO_4^- \rightleftharpoons HNO_3 + 2H_2SO_4$$

(*b*) Nitrosyl hydrogen sulphate formed,

$$NO^+ + HSO_4^- \rightleftharpoons NOHSO_4$$

Stage IV (16 to 45 mol. % and crystallisation of nitrosyl hydrogen sulphate). Further compound formation. Dilution of medium by molecular N_2O_4. Further increase in viscosity.

Speculation on the mechanism and intermediates involved in these equilibria is not yet profitable.

There is reason to suppose that the conductivity curve of the solutions in selenic acid has a similar explanation. Clearly, however, the possible concentration of completely ionised dinitrogen tetroxide is smaller in our selenic acid than in sulphuric acid, but whether our selenic acid was absolute is uncertain. If it contained moisture, the conductivity recorded for it will be too high and the true curve would be more like that of sulphuric acid. Nevertheless, since Ingold, Millen, and Poole (*Nature*, 1946, **158**, 480) found nitric acid in selenic acid to give NO_2^+ and $HSeO_4^-$, there is justification for assuming the following equilibria, particularly as crystals of nitrosyl hydrogen selenate are obtained :

$$N_2O_4 + 3H_2SeO_4 \rightleftharpoons NO_2^+ + NO^+ + H_3O^+ + 3HSeO_4^- \rightleftharpoons HNO_3 + 2H_2SeO_4$$
$$NO^+ + HSeO_4^- \rightleftharpoons NOHSeO_4$$

We have not measured densities and viscosities, but appearance leads us to think they follow a similar course to those involving sulphuric acid.

The conductivity of our phosphoric acid suggests that it was near absolute and that the difference in the conductivity curve from that of sulphuric acid is real. In particular there is only a short range of colourlessness; within that range the process of ionisation may well be

$$N_2O_4 + 3H_3PO_4 = NO_2^+ + NO^+ + H_3O^+ + 3H_2PO_4^-$$

We do know that the viscosity increases with the addition of dinitrogen tetroxide, and especially so at higher concentrations.

As all the experiments were done above laboratory temperature, the nitrogen peroxide contained nitrogen dioxide as well as dinitrogen tetroxide. But, since every solution is colourless when sufficiently dilute, it is probable that the presence of a little NO_2 does not seriously upset the course the reaction follows when N_2O_4 is present alone.

Experimental

Preliminary.—Sulphuric acid was shown to absorb about 0·9 mol. of N_2O_4 per mol. of H_2SO_4. The solution appeared colourless up to about 7 mol. %, gradually darkened, and finally deposited $NOHSO_4$ at about 48 mol. % of N_2O_4. Nitrosyl hydrogen sulphate was also obtained on adding sulphuric acid to dinitrogen tetroxide (Found : N, 10·4; S, 24·9%; equiv., 41·9. Calc. for $NOHSO_4$: N, 11·0; S, 25·2%; equiv., 42·3); m. p. 83—84° (decomp.).

Selenic absorbed about 0·75 mol. of N_2O_4 per mol. of H_2SeO_4. Up to about 7 mol. % it remained colourless, gradually darkened and finally deposited $NOHSeO_4$ at about 40 mol. % of N_2O_4. Nitrosyl hydrogen selenate was also obtained by adding selenic acid to the tetroxide (Found : N, 7·5; Se, 46·1%; equiv., 59·0. Calc. for $NOHSeO_4$: N, 8·0; Se, 45·4%; equiv., 58·0); m. p. 85—86° (decomp.).

Phosphoric acid absorbed about 0·13 mol. of N_2O_4 per mol. of H_3PO_4. The solution became

yellow at a low concentration; no solid separated from mixtures with either component in excess even on strong cooling.

The three acids, when saturated with dinitrogen tetroxide, were immiscible in it. In the case of sulphuric acid, the layer of tetroxide which separated was shown to contain nitric acid, but no sulphuric acid.

The solids were separated from their mother-liquors by filtration through a glass frit, and dissolved in water under conditions which avoided loss of oxides of nitrogen. In the solution nitrogen was determined by reduction with Devarda's alloy in a Kjeldahl apparatus, sulphur by precipitation as barium sulphate, selenium by reduction to the element. Direct titration of an aqueous solution, using carbonate-free 0·1N-sodium hydroxide with methyl-red as indicator, gave the acid equivalent weight. The $NOHSeO_4$ was less easy to isolate and showed slight decomposition at the ordinary temperature. Both nitrosyl hydrogen sulphate (see Elliott, *J.*, 1926, 1219) and selenate (Meyer and Wagner, *J. Amer. Chem. Soc.*, 1922, **44**, 1032) are known.

Materials.—Absolute sulphuric acid was made by dilution of high-quality dilute oleum with conductivity water until the minimum conductivity was attained. Selenic acid (B.D.H.) was used without further purification, the sample with the lowest conductivity being chosen. The same applies to phosphoric acid which was B.D.H., 100%. Both are solid, but as they readily supercool after melting, conductivities on the liquids at 25° could be measured. Crude dinitrogen tetroxide from copper and concentrated nitric acid was passed with oxygen over phosphoric oxide and condensed on to phosphoric oxide at −180°. After standing, this material was fractionated in a vacuum by bulb-to-bulb distillation with rejection of head and tail fractions, and stored in tubes fitted with break-seal joints.

Manipulation and Measurement.—To avoid atmospheric moisture, the materials were handled and the mixtures made in a vacuum, or under air dried by phosphoric oxide and protected with phosphoric oxide guard tubes.

The measurement of conductivity will be dealt with in a later paper; we merely record that results were accurate to ±0·00002 ohm^{-1} cm.$^{-1}$ at 25·00° ± 0·01°. The densities were determined by weighing a standard volume of liquid under conditions which protected it from atmospheric moisture. An accuracy of ±0·01 g. per c.c. was sufficient for our purpose and more is not claimed. The viscosities except for those of very dilute solutions (used in Fig. 3) are on an arbitrary scale, being for comparative purposes only.

Results.—The specific conductivities, κ, in ohms^{-1} cm.$^{-1}$ at 25° for solutions of dinitrogen tetroxide in the three acids are given in the Tables.

Expt. 1				Expt. 2					
Concn. (mol. %)	100 κ	Concn. (mol. %)	100 κ	Concn. (mol. %)	100 κ	Concn. (mol. %)	100 κ	Concn. (mol. %)	100 κ
Sulphuric acid.									
47·56	2·551	1·808	6·299	42·66	3·246	6·871	9·956	2·077	7·215
35·02	4·938	0·8065	3·807	32·11	5·282	6·113	10·15	1·291	5·426
25·56	6·925	0·3746	2·313	20·24	7·246	5·655	10·30	0·6440	3·725
14·54	8·736	0·1433	1·438	9·593	9·467	3·921	9·409	0·0000	1·045
7·181	10·26	0·0000	1·045	8·611	9·595	3·031	8·559		
Selenic acid.									
Expt. 1				Expt. 2		Expt. 3		Expt. 4	
43·29	2·919	13·46	7·733	27·60	4·654	19·48	6·372	15·38	7·272
39·37	3·082	9·464	8·355	18·01	6·653	9·033	7·912	7·921	8·485
35·31	3·455	4·699	8·993	10·56	7·818	4·205	8·922	3·821	8·864
30·94	4·414	0·5545	9·576	5·371	8·887	2·246	9·141	2·266	9·233
26·73	5·184	0·3120	9·625	1·075	9·481			1·280	9·430
20·46	6·439	0·0000	9·105					0·6146	9·569
16·64	7·174							0·2706	9·624
								0·0000	9·092
Phosphoric acid.									
11·50	3·132	2·43	4·803	0·893	5·054	0·135	5·216	0·013	5·207
6·94	4·084	1·69	4·944	0·500	5·126	0·0595	5·232	0·000	5·192
4·53	4·483	1·36	4·982	0·252	5·170	0·0305	5·220		

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Preparation and Some Physical Properties of Sulphur Tetrafluoride.

By F. Brown and P. L. Robinson.

[Reprint Order No. 6375.]

Previous work on sulphur tetrafluoride is summarised. A reliable, if somewhat tedious, method for its preparation from the elements and its subsequent purification are described. Its melting and boiling point, density, surface tension, and vapour pressure have been determined. These data are shown in relation to the properties of the tetrafluorides of selenium and tellurium.

Besides sulphur hexafluoride and disulphur decafluoride, three others, collectively referred to as lower fluorides—tetrafluoride, difluoride, and disulphur difluoride—are mentioned in the literature. Some or all of the latter are formed in most of the reactions where the hexafluoride, or its first homologue, is the main product. Invariably these lower fluorides accompany one another when the aim is to produce any one of them. According to Trautz and Ehrmann (*J. prakt. Chem.*, 1935, **142**, 79) disulphur difluoride readily decomposes to sulphur difluoride, though Dubnikoff and Zorin (*J. Gen. Chem., U.S.S.R.*, 1947, **17**, 185), who made it by the action of excess of sulphur on silver fluoride at 200°, say that decomposition takes place above that temperature. We are inclined to think, with Trautz and Ehrmann (*loc. cit.*), that neither of these fluorides has yet been obtained pure, although a m. p., −105·5°, and b. p., −99°, have been reported for disulphur difluoride (Centnerszwer and Strenk, *Ber.*, 1925, **58**, 814).

The present communication deals with sulphur tetrafluoride; as the compound has been so recently described as "almost certainly wrong" (Sidgwick, "The Chemical Elements and their Compounds," Oxford, 1950, Vol. II, p. 943), a brief review of the facts is not inappropriate. Ruff and Thiel (*Ber.*, 1905, **38**, 549) failed to get it by the action of hydrogen fluoride with sulphur nitride or tetrachloride, or of the latter with titanic or stannic fluoride, or arsenic trifluoride, but Ruff and Heinzelmann (*Z. anorg. Chem.*, 1911, **72**, 63) appear, from the properties they reported, to have had a material which contained some tetrafluoride, but they do not seem to have recognised its presence. Heating sulphur with mercury fluorides (Ruff and Bahlau, *Ber.*, 1918, **51**, 1752), iodine heptafluoride (Ruff and Keim, *Z. anorg. Chem.*, 1930, **193**, 176), or fluorine (Schumb and Gamble, *J. Amer. Chem. Soc.*, 1930, **52**, 4302; Yost and Claussen, *ibid.*, 1933, **55**, 885; Denbigh and Whytlaw-Gray, *J.*, 1934, 1347) gave unidentified lower fluorides. Examination of the gaseous product of the reduction of cobalt trifluoride with sulphur by Fischer and Jaenckner (*Z. angew. Chem.*, 1929, **42**, 810) led them to believe it was the tetrafluoride. Their results were not reproducible; and, later, Luchsinger (Diss., Breslau, 1936) showed that the metal fluorides when heated with sulphur produce mixtures of all the above-named fluorides of sulphur in proportions depending on the kind of fluoride, the ratio of fluoride to sulphur used, and the rate at which the reaction proceeds. Silvey and Cady (*J. Amer. Chem. Soc.*, 1950, **72**, 3624) separated the tetrafluoride from the breakdown products of $CF_3{\cdot}SF_5$ in a high-voltage discharge (Linn and Geballe, *J. Appl. Phys.*, 1950, **21**, 592). Disulphur decafluoride is decomposed by heat to a mixture of the hexa- and tetra-fluoride (Trost and McIntosh, *Canad. J. Chem.*, 1951, **29**, 508). Silvey and Cady (*J. Amer. Chem. Soc.*, 1952, **74**, 5792) and Tyczkowski and Bigelow (*ibid.*, 1953, **75**, 3523) both found the tetrafluoride present when carbon disulphide is mildly fluorinated with the element. Very recently, Schmidt (*Monatsh.*, 1954, **85**, 452) obtained a yellow solid on heating disulphur dibromide and iodine pentafluoride together in a steel bomb; this, when heated with copper turnings in a copper bomb, gave the tetrafluoride. Melting and boiling points of the materials believed to have been sulphur tetrafluoride, so far as reported, are set out with our own for comparison:

	m. p.	b. p.
1911, Ruff and Heinzelmann	−135°	−40°
1936, Luchsinger	−125·0	−40·0
1953, Tyczkowski and Bigelow	−122	−38
1955, Present work	−121·0	−40·4

In seeking a method giving uniquely the tetrafluoride, sulphides of silver, cadmium, cobalt, mercury, bismuth, zinc, and iron were treated with fluorine in various dilutions and at various temperatures. The solid solution of sulphur and iodine was also employed, and attempts were made to reduce iodine pentafluoride with sulphur. All these reactions gave sulphur hexafluoride with, in most cases, a little of what could be designated lower fluorides. The success or otherwise of an experiment was made manifest by the behaviour of the product: if the solid were allowed to sublime at atmospheric pressure, the amount of low-boiling liquid remaining proved a sure indication of the proportion of lower fluorides. Unfortunately, the proportions were so low as to render none of these methods worth pursuing, and we turned to a study of the fluorine–sulphur reaction. Enough had, however, been observed to make it clear that the working temperature was probably the most significant factor, and that, under any forseeable circumstance, a mixture containing some hexafluoride would be produced.

When fluorine and sulphur react the temperature can easily reach the point of inflammation, but even at much lower temperatures the major product is the highest fluoride. At about −150° the rate of reaction becomes impossibly slow and, according to our observations, is not productively useful below about −75°. To keep this optimum temperature in the reaction zone we tried a number of devices submerged in cooling baths: glass and metal columns packed with sulphur alone, and with nickel shot and sulphur; flasks on the inner surface of which sulphur had been caused to set as a continuous coat; flasks with a sublimate of sulphur on the inner surface. The columns, though sometimes as narrow as 0·5 in., invariably blocked up, either by reason of a partial melting of the sulphur particles, or through a deposit of sulphur from solution in the fluorides, or from the decomposition of disulphur difluoride. Its thermal conductivity is so low that a frozen layer of massive sulphur could not be effectively cooled, and the yield of lower fluorides proved small. Hence we turned to the method developed in this laboratory for the preparation of selenium tetrafluoride (*J.*, 1952, 1231), namely, the fluorination of sulphur in the form of a sublimate on a glass surface. In the case of selenium, almost pure tetrafluoride is produced when the temperature is kept about 0°; for sulphur −75° is required, and the proportion of tetrafluoride is estimated at 40% of the total yield. We had found that the presence of moisture in any preparation invariably led to the formation of some thionyl fluoride, SOF_2, and sublimation of the sulphur in a vacuum proved a means of ensuring a sufficient drying of the element. Fluorine, largely diluted with nitrogen, was employed; and the product, condensed by means of liquid oxygen, was subjected to a trap-to-trap distillation in a vacuum. There was some separation of sulphur either from solution or by the decomposition of disulphur difluoride at the later stages when the low-boiling head fraction containing hexa- and tetra-fluoride had been largely removed to leave a tail fraction consisting mainly of disulphur decafluoride (b. p. +29°). The former was split by fractionation in a Podbielniak column (*Ind. Eng. Chem., Anal. Ed.*, 1931, **3**, 177; 1933, **5**, 119) working at something over two atm. pressure. After the removal of hexafluoride (b. p. −53°/2 atm.), a long refluxing was necessary to separate the thionyl fluoride, SOF_2 (b. p. −43·8°), from the tetrafluoride (b. p. −40·4°). The final product was characterised by measurement of vapour density and by determination of sulphur and fluorine. The almost complete freedom of the material from sulphur oxyfluorides and silicon tetrafluoride was shown by the infrared spectrum, and the Raman spectrum gave no evidence of these or of sulphur hexafluoride.

The following physical properties were determined, and Luchsinger's values, where available, are given in parenthesis:

Density (g. cm.$^{-3}$) at 200° K = 1·9191 (1·9333)
Density (g. cm.$^{-3}$) at T° K (170—200° K) = $2{\cdot}5471 - 0{\cdot}00314T$ ($2{\cdot}6253 - 0{\cdot}00346T$)
Coeff. of cu. expansion (c.c./c.c./°C) (170—200° K) = 0·00170
Melting point (° C) = −121·0° ± 0·5° (−125·0°)
Boiling point (° C) (from v.p.) = −40·4° (−40·1°)
Surface tension (dynes cm.$^{-1}$) at 200° K = 25·70
Surface tension (dynes cm.$^{-1}$) at T° K (190—230° K) = $61{\cdot}36 - 0{\cdot}1783T$

Vapour pressure (mm.) at 200° K = 80·8 (120·6)
Vapour pressure (mm.) at T° K (160—224° K), $\log P = 8{\cdot}8126 - 1381/T$ (7·7068 $-1125{\cdot}1/T$)

The latent heat of vaporisation is 6320 cal. mole^{-1} and the Trouton's constant 27·1. From the relation $T_{b.p.}/T_c \sim 0{\cdot}67$ a critical temperature of 74° is indicated which is not far from the figure of 71°, the temperature at which the surface tension is zero. The relation between the tetrafluorides of sulphur and selenium (values mainly from Peacock, *J.*, 1953, 3617) is shown below and it may be noted that Trouton's constant is high in both cases, suggesting some association.

	SF_4	SeF_4
Melting point (° c)	−121°	9·5°
Boiling point (° c)	−40·4°	106°
Approx. critical temp. (° c)	70°	290°
Trouton's constant	27·1	30·0
Molar latent heat of vaporisation (cal.)	6,320	11,240
Surface tension at b. p. (dynes cm.$^{-1}$)	19·85	25·8

These data may be a guide to some of the physical properties of tellurium tetrafluoride, all of which, by reason of its attack on most materials, are difficult to ascertain. Earlier work in these laboratories indicated a melting point of a little over 100° and a boiling point about 250°. These are about the values that might be expected from the corresponding figures for the first two members of the series.

Experimental

Preparation.—After much exploratory work with various reactions we found the most promising to be that between fluorine and sulphur, and the most favourable conditions to be, the former well diluted with nitrogen, and the latter as a sublimate on a glass surface at −75°. The absence of oxygen and moisture is obligatory because thionyl fluoride is easily formed, either by a primary or secondary reaction, and is difficult to separate from the tetrafluoride. To meet these conditions an all-Pyrex glass train consisting of two conical flasks in series followed by a number of cylindrical traps and a break-seal vessel was used. This was well flamed under a vacuum with repeated fillings of oxygen-free nitrogen. Good quality sulphur, after being kept molten in a vacuum for some time to allow the release of moisture and gases, was deposited as a thin sublimate on the surfaces of the two conical flasks. Further to reduce the risk of introducing oxygen, the electrolytic fluorine cell was run for 2 hr. before the gas, after passing over sodium fluoride and being cooled to −180°, was used. The fluorine, at 850 c.c. per hr., diluted with 3 times its volume of nitrogen, previously freed from oxygen, dried over phosphoric oxide, and cooled to −180°, was passed through the train, the two flasks being submerged in ethanol–solid carbon dioxide at −75°, and the exit protected against ingress of moisture. The mild, low-temperature fluorination caused a colourless liquid to appear on the surface of the sulphur; most of this remained there and the rest was retained in the first trap beyond the reaction flasks, which was at −180°. At the end of a run, usually lasting 24 hr., the fluorine stream was stopped, and the flasks were allowed slowly to warm, with the nitrogen stream maintained; as a result the product containing 40% of sulphur tetrafluoride was all collected in the first trap. The reaction flasks were then sealed off and the rest of the train evacuated, the mixture of fluorides being kept frozen.

Purification.—The bulb-to-bulb vacuum-fractionation which followed, and during which a slight white deposit of sulphur appeared on the glass surfaces, was designed to remove as a tail fraction of about 2 c.c. most of the disulphur decafluoride (b. p. +29°). The rest of the material, about 22 c.c., was collected in a break-seal vessel for transference to the boiler of a Podbielniak still (*loc. cit.*). The column (67 cm. × 6 mm.) of the still was fitted with a metal spiral (5 turns per cm. of 24 s.w.g. wire) and surrounded by a sleeve-type, silvered vacuum-jacket. Liquid to provide the reflux was condensed by surrounding the head of the column with a small double-walled copper jacket which was cooled by blowing liquid air into the outer annulus whence it passed through the inner annulus to escape. The operating temperature was measured to ±0·5° by means of a calibrated base-metal thermocouple used in conjunction with a galvanometer. Since the material at this stage in the purification (except for the trace of silicon tetrafluoride still present) does not attack the metal, a mercury manometer reading to ~3 atm. was used for the pressure measurements. We found that the occasional, ordinary glass stopcock

which greatly facilitated the operation of the column could be safely used up to this pressure, provided it was lubricated with hard fluorocarbon grease. As a precaution against its being blown out, the plug was secured by a stout rubber ring. Troublesome bumping was avoided by having a piece of capillary in the boiler.

Our practice, after the removal of sulphur hexafluoride had been signalled by a sharp rise in temperature at the still-head, was to reduce the pressure from 1800 to 800 mm. and, by a prolonged fractionation at this pressure, to get rid of the small amount of thionyl fluoride which was always present, and for which the oxygen is obtained from a slight attack on the glass mainly during preparation. In none of the distillations did we have any evidence of the presence of a second impurity at this stage, which led us to think that the amount of sulphur difluoride, if any, was small.

Characterisation.—Measurements of vapour density indicated a molecular weight of 108·8 ± 0·5 (SF_4 requires 108·1). For analysis a sample was dissolved by opening a bulb in a solution of 2·5% sodium hydroxide solution and 30% hydrogen peroxide; excess of the latter was destroyed by boiling, and the solution was made up to 100 c.c. An aliquot part was acidified and the sulphur determined as barium sulphate. A second aliquot part was passed through the cation-exchange resin, Zeo-Carb 225H, and the resulting aqueous solution of hydrogen fluoride and sulphuric acid was titrated hot with 0·1N-sodium hydroxide (Found: S, 30·36; F, 69·11. SF_4 requires S, 29·67; F, 70·33%).

Physical Properties.—Density was measured by observing the liquid level of a known weight of sulphur tetrafluoride (weighed as vapour; see *J.*, 1955, 2230, Fig. 1*a*) in the fine stem of a thermometer-type bulb, previously calibrated by means of mercury. The plot of density against absolute temperature is a straight line, of slope $-3·14 \times 10^{-3}$.

Temp. (c)	−78·7°	−80·7°	−82·7°	−84·7°	−86·9°	−87·4°	−91·4°	−96·1°
(K)	194·5°	192·5°	190·5°	188·5°	186·3°	185·8°	181·8°	177·1°
Density (g./c.c.)	1·9358	1·9423	1·9377	1·9547	1·9618	1·9633	1·9777	1·9931
$10^3 \times$ Slope	−3·14	−3·14	−3·20	−3·14	−3·14	−3·14	−3·13	−3·13

The melting point was observed by noting the fall of a glass style through the melting solid (Stock, *Ber.*, 1917, **50**, 156) contained in a sealed vessel. This was submerged in a well-stirred bath of ether cooled with liquid nitrogen in a Dewar vessel, the temperature being measured by means of a copper–constantan thermocouple and a potentiometer. An accuracy of ± 0·5° is claimed.

Surface tension was measured by using two capillary tubes of different, known diameters mounted with the liquid in a sealed vessel (Mills and Robinson, *J.*, 1927, 1823). The apparatus was completely submerged in a low-temperature bath in an unsilvered Dewar flask through which the difference in capillary rise was observed by means of a cathetometer. An accuracy of ±0·2 dyne $cm.^{-1}$ is claimed; a plot against absolute temperature is a straight line, of slope 0·1783.

Temp. (c)	−76·8°	−64·7°	−57·2°	−50·0°	−45·5°
(K)	196·4°	208·5°	216·0°	223·2°	227·7°
Surface tension (dynes $cm.^{-1}$)	26·39	23·84	22·80	21·57	20·77
Slope	0·1781	(0·1800)	0·1785	0·1783	0·1783

Vapour pressure, as shown by preliminary work, is sensitive to impurity, whether this be the result of inadequate fractionation or from keeping the material too long in contact with glass. For this reason, sulphur tetrafluoride, specially purified, was used at once, with vacuum-transfer and rigorous drying of all apparatus. The container, a glass bulb, was directly attached to a mercury manometer, alongside which stood a barometer. The ether-bath fixing the temperature of the tetrafluoride was well stirred and kept to within ±0·1° of the required temperatures, a copper–constantan thermocouple and a potentiometer being used for the measurements. Besides calibration at fixed points, accuracy received a further check by observing the vapour

Temperature		Pressure			Temperature		Pressure		
°C	°K	mm.	log	Slope	°C	°K	mm.	log	Slope
−112·3	160·9	1·56	0·1931	−1387	−66·3	206·9	142·46	2·1538	−1378
−102·7	170·5	5·14	0·7110	−1382	−59·8	213·4	217·10	2·3367	−1382
− 92·0	181·2	16·56	1·2191	−1376	−54·7	218·5	299·58	2·4766	−1385
− 83·6	189·6	36·78	5·5657	−1374	−49·2	224·0	397·20	2·5990	−1392
− 75·0	198·2	74·36	1·8714	−1376				Mean	−1381

pressures of ethylene, dichlorodifluoromethane, and trichlorofluoromethane between −130° and +10°. The heights of mercury in the manometer and barometer were read to ±0·02 mm. by means of a cathetometer. An accuracy of ±0·5 mm. is claimed for the vapour pressures.

The authors are indebted for the spectral evidence of the purity of their sulphur tetrafluoride to Mr. R. E. Dodd (infrared) and Dr. L. A. Woodward (Raman). They thank Imperial Chemical Industries Limited, General Chemicals Division, Widnes, for the use of the fluorine cell, and Durham County Education Committee for a maintenance grant (F. B.).

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A Direct Transformation of cyclo*Hexanones into* bicyclo[5 : 3 : 0]*Dec-7-en-9-ones.*

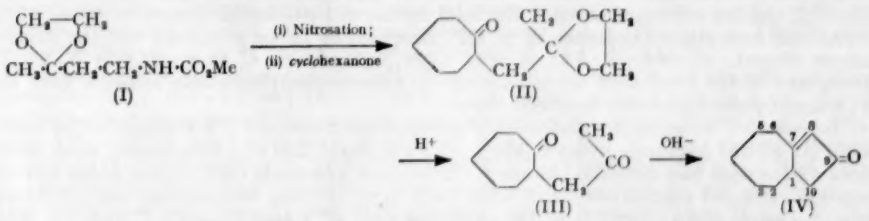
By A. M. ISLAM and R. A. RAPHAEL.

[Reprint Order No. 6307.]

By reaction with 1-diazo-3 : 3-ethylenedioxybutane followed by acid hydrolysis and aldolisation, *cyclo*hexanones are converted into *bicyclo*-[5 : 3 : 0]dec-7-en-9-ones in a substantially one-step operation.

ALTHOUGH many routes have been used for the conversion of *cyclo*heptanone itself into *bicyclo*[5 : 3 : 0]decane derivatives the methods become both tedious and ambiguous when applied to the production of such derivatives with substituents in the seven-membered ring. To overcome these difficulties a method has now been evolved which entails the ring expansion of a *cyclo*hexanone with a diazo-compound of such a nature that the resulting *cyclo*heptanone possesses a side-chain capable of interaction with the ring carbonyl group to form the required five-membered ring.

The diazo-compound used was 1-diazo-3 : 3-ethylenedioxybutane. Addition of phthalimide to methyl vinyl ketone, followed by ketalisation of the resulting 4-phthalimidobutan-2-one with ethylene glycol, gave 3 : 3-ethylenedioxy-1-phthalimidobutane. This was converted by hydrazine into 1-amino-3 : 3-ethylenedioxybutane whence methyl chloroformate afforded the required urethane precursor (I). As these reactions were



inconvenient on a large scale, ethyl lævulate was converted into its ethylene ketal which was then transformed into its hydrazide and azide in the usual fashion; treatment with methanol converted the last derivative into the urethane (I).

Treatment of the nitroso-derivative of urethane (I) with *cyclo*hexanone and potassium carbonate in methanol (the usual solvent for such ring expansions) caused vigorous evolution of the expected volume of nitrogen, but only unchanged *cyclo*hexanone was isolated. This was due to the immediate reaction of the diazo-compound formed with the solvent. When ethanol replaced methanol, ring expansion ensued, giving the *cyclo*heptanone (II). This seems to be one of the rare cases where the small difference in acidity between ethanol and methanol manifests itself (methanol, pK_a 16; ethanol, pK_a 18). Acid hydrolysis of the ketal (II) gave 2-acetonyl*cyclo*heptanone (III) which underwent a smooth base-catalysed internal aldol condensation to give *bicyclo*[5 : 3 : 0]dec-7-en-9-one (IV). On the preparative scale, isolation of the pure intermediates (II) and (III) is unnecessary.

Application of the method to 4-methyl- and 4-*iso*propyl-*cyclo*hexanone produced the 4-substituted *bicyclo*[5 : 3 : 0]dec-7-en-9-ones. Although these compounds contain two asymmetric centres, only one homogeneous product was obtained. This, however, is to be expected as the presence of a carbonyl group adjacent to one of the asymmetric

centres in the intermediates corresponding to (II) and (III) ensures stereomutation to the more stable geometrical isomer. Unexpectedly, only one product was also obtained from 2-methyl*cyclo*hexanone, although in this case the incursion of position isomerism is possible, depending on which side of the carbonyl group the ring expansion takes place. It is suggested that the product is 6-methyl*bicyclo*[5 : 3 : 0]dec-7-en-9-one, the expansion ensuing at the less sterically hindered side of the carbonyl group. This is borne out by the finding that 2 : 6-dimethyl*cyclo*hexanone did not undergo ring expansion under the same conditions.

Catalytic reduction of *bicyclo*[5 : 3 : 0]dec-7-en-9-one (IV) gave a homogeneous ketone (semicarbazone, m. p. 198—199°), and lithium in liquid ammonia produced a stereoisomer (semicarbazone, m. p. 221—223°). The latter tallies with a known ketone of this structure but unspecified configuration (Plattner, Fürst, and Jirasek, *Helv. Chim. Acta*, 1946, **29**, 730, 740, report m. p. 222—223° for its semicarbazone). Although it can be said that this is the more thermodynamically stable isomer (Barton and Robinson, *J.*, 1954, 3045) it is difficult from purely conformational reasoning to determine its geometrical configuration. This assignment is being studied synthetically.

Experimental

4-Phthalimidobutan-2-one.—Phthalimide (18 g.), freshly distilled methyl vinyl ketone (8·7 g.), and benzyltrimethylammonium hydroxide (3 c.c.) in ethyl acetate (70 c.c.) were stirred at the b. p. for 30 min. Evaporation to dryness under reduced pressure gave the *ketone* (24 g., 90%) which crystallised from ethanol in rhombs, m. p. 112° (Found: C, 66·5; H, 5·25; N, 6·7. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·05; N, 6·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange prisms, m. p. 176° (Found: C, 54·6; H, 3·4; N, 17·75. $C_{18}H_{15}O_6N$ requires C, 54·45; H, 3·7; N, 17·65%).

3 : 3-*Ethylenedioxy*-1-*phthalimidobutane* (2-*Methyl*-2-3′-*phthalimidopropyl*-1 : 3-*dioxolan*).—The above ketone (15 g.), ethylene glycol (6·5 g.), and toluene-*p*-sulphonic acid (0·2 g.) in dry benzene (300 c.c.) were heated under reflux for 3 hr. with automatic water separation. The cooled benzene solution was washed with sodium carbonate solution and water, and dried ($MgSO_4$), and the solvent removed. The solid residue of 1-*phthalimido-compound* (15 g., 83%) crystallised from ethanol in prisms, m. p. 122°, depressed by 20° on admixture with the starting ketone (Found: C, 64·8; H, 5·7; N, 5·2. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·7; N, 5·3%). Treatment of the ketal with warm alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave the 2 : 4-dinitrophenylhydrazone described above.

1-*Amino*-3 : 3-*ethylenedioxybutane* (2-3′-*Aminopropyl*-2-*methyl*-1 : 3-*dioxolan*).—The above ketal (15 g.) and hydrazine hydrate (100%; 3 g.) in water (250 c.c.) were heated under reflux until all the solid had dissolved (50 min.). 2N-Sodium hydroxide (25 c.c.) was added and the solution extracted continuously with ether for 3 days. Drying, evaporation, and distillation gave the *amine* (5·6 g., 79%), b. p. 121—122°/100 mm., n_D^{22} 1·4460 (Found: C, 54·6; H, 9·75; N, 10·3. $C_6H_{13}O_2N$ requires C, 54·95; H, 10·0; N, 10·7%). The 2 : 4-*dinitrophenyl derivative* crystallised from ethanol in yellow prisms, m. p. 116—118° (Found: C, 48·65; H, 5·2; N, 14·2. $C_{12}H_{15}O_6N_3$ requires C, 48·5; H, 5·1; N, 14·1%).

3 : 3-*Ethylenedioxybutanecarboxyhydrazide.*—A mixture of ethyl 3 : 3-ethylenedioxybutanecarboxylate (Kühn, *J. prakt. Chem.*, 1940, **156**, 103) and hydrazine hydrate (100%; 35 g.) was heated under reflux for 4 hr.; the mixture became homogeneous after 45 min. Distillation gave the *hydrazide* (80 g., 87%), b. p. 142°/0·4 mm., which solidified to extremely hygroscopic crystals, m. p. *ca.* 34° (Found: C, 46·65; H, 7·7; N, 16·3. $C_7H_{14}O_3N_2$ requires C, 48·2; H, 8·0; N, 16·1%). The *α-methylbenzylidene derivative*, prepared by heating the hydrazide with acetophenone, crystallised from ethanol in needles, m. p. 99—100° (Found: C, 65·35; H, 6·7; N, 10·35. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·2; N, 10·15%).

3 : 3-*Ethylenedioxy*-1-*methoxycarbonylaminobutane* (2-3′-*Methoxycarbonylaminopropyl*-2-*methyl*-1 : 3-*dioxolan*) (I).—(*a*) A solution of the hydrazide (60 g.) and sodium nitrite (60 g.) in water (150 c.c.) was covered with ether (120 c.c.) and cooled to −5°. An ice-cold solution of concentrated sulphuric acid (33 g.) in water (120 c.c.) was added, with shaking, at such a rate that the temperature remained between −5° and 0°. Then the ether layer was decanted and the aqueous layer washed twice with fresh ether. The combined extracts were dried (Na_2SO_4), methanol (100 c.c.) was added, and the ether was distilled off. The resulting methanolic

solution was heated under reflux for 2 hr. Removal of the solvent and distillation gave the water-soluble *urethane* (I) (33 g., 51%), b. p. 98—100°/0·4 mm., n_D^{18} 1·4555 (Found: C, 50·3; H, 7·6; N, 7·45. $C_8H_{15}O_4N$ requires C, 50·8; H, 7·9; N, 7·4%). A preparation on four times this scale gave a similar yield. The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in light yellow needles, m. p. 121° (Found: C, 44·5; H, 4·8; N, 21·6. $C_{15}H_{18}O_8N_6$ requires C, 44·3; H, 4·6; N, 21·5%).

(*b*) To a stirred solution of 1-amino-3 : 3-ethylenedioxybutane (1·3 g.) in dry ether (15 c.c.) at 0° were added dropwise and simultaneously methyl chloroformate (1 g.) and a solution of sodium hydroxide (0·4 g.) in water (4 c.c.). After 15 min. the product was isolated with ether. Drying (K_2CO_3), evaporation, and distillation gave the above urethane (1·6 g., 84%), b. p. 148—150°/16 mm., n_D^{22} 1·4538, which gave a 2 : 4-dinitrophenylhydrazone identical with that described under (*a*).

A mixture of the urethane (10 g.), sodium nitrite (60 g.), crushed ice (10 g.), and water (80 c.c.) was covered with ether (30 c.c.) and cooled to 0°. A cold solution of concentrated nitric acid (20 c.c.) in water (30 c.c.) was run in slowly with occasional shaking from a dropping funnel, the end of which was immersed in the aqueous layer; the temperature was kept below 5°. The bluish-green ether layer was removed and the aqueous layer washed twice with fresh ether. The combined extracts were washed with chilled concentrated potassium hydrogen carbonate solution and dried (Na_2SO_4) at 0°. Removal of the ether at room temperature under reduced pressure gave the *N*-nitrosourethane as a pink viscous oil (10 g.) which decomposed on attempted distillation. This product was used as such for the following ring expansions.

2-(2 : 2-*Ethylenedioxypropyl*)cyclo*heptanone* (2-*Methyl*-2-2′-*oxo*cyclo*heptyl*-1 : 3-*dioxolan*) (II).—The *N*-nitrosourethane (10 g.) was added dropwise to a stirred mixture of *cyclo*hexanone (6 g.), dry ethanol (20 c.c.), and freshly ignited, powdered potassium carbonate (3 g.) at such a rate that the temperature of the mixture did not exceed 28°. The colour deepened gradually to orange and 900 c.c. of nitrogen were collected after 5 hr. (theor., 1030 c.c.). After filtration and evaporation of the ethanol, water was added and the product was isolated with ether. Distillation gave the ketone (II) (6 g.), b. p. 94—96°/0·3 mm., $n_D^{20\cdot5}$ 1·4747. The product tenaciously retained a small quantity of a nitrogen-containing impurity which resulted in inaccurate analytical figures.

2-*Acetonyl*cyclo*heptanone* (III).— A solution of the *cyclo*heptanone (II) (4 g.) in ethanol (20 c.c.) and 5% sulphuric acid (5 c.c.) was set aside overnight. Dilution with water and isolation by means of ether gave 2-*acetonyl*cyclo*heptanone* (2·5 g., 80%), b. p. 128°/12 mm., n_D^{19} 1·4700 (Found: C, 70·9; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%).

bicyclo[5 : 3 : 0]*Dec-7-en-9-one*.—A mixture of the diketone (III) (2 g.), aqueous potassium hydroxide (5%; 150 c.c.), and ethanol (10 c.c.) was heated under reflux for 3 hr. Steam-distillation and extraction of the distillate with ether gave the bicyclic *ketone* (1·3 g., 72%), b. p. 118—120°/16 mm., n_D^{19} 1·5212 (Found: C, 79·6; H, 8·9. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%). Light absorption in EtOH: max. at 233 (ε 12,600) and 289 mμ (ε 190). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol–ethyl acetate in red needles, m. p. 184—185° (Lloyd and Rowe, *J.*, 1953, 3718, give m. p. 185°) (Found: C, 58·3; H, 5·5; N, 17·1. Calc. for $C_{16}H_{18}O_4N_4$: C, 58·2; H, 5·5; N, 17·0%). Light absorption in EtOH: max. at 388 mμ (ε 26,700). The *semicarbazone* crystallised from ethanol in plates, m. p. 220—222° (Found: N, 20·0. $C_{11}H_{17}ON_3$ requires N, 20·2%).

Combined Ring Expansion and Cyclisation Procedure.—The *N*-nitrosourethane (10 g.) was added to a stirred mixture of the relevant *cyclo*hexanone (6 g.), dry ethanol (20 c.c.), and ignited potassium carbonate (3 g.) at such a rate that the mixture remained between 20° and 30°. After 5 hr. the potassium carbonate was filtered off, 5% sulphuric acid (10 c.c.) added, and the mixture set aside overnight. Saturated ammonium sulphate solution was then added and the organic layer isolated with ether. After removal of the solvent the product was heated under reduced pressure to remove any unchanged *cyclo*hexanone. The residue was treated with potassium hydroxide solution as described above and the resulting bicyclic ketone isolated in the same way.

Applied to *cyclo*hexanone itself this process gave a very reproducible yield of *bicyclo*-[5 : 3 : 0]dec-7-en-9-one (28% based on *N*-nitrosourethane). 4-Methyl*cyclo*hexanone gave the 4-*methyl homologue* (32%), b. p. 124°/16 mm. (Found: C, 80·4; H, 9·4. $C_{11}H_{16}O$ requires C, 80·5; H, 9·7%). The chromatographically homogenous 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol–ethyl acetate in red needles, m. p. 155—157° (Found: C, 59·1; H, 6·1; N, 16·3. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·8; N, 16·3%); light absorption in EtOH: max. at 388 mμ (ε 28,900). The *semicarbazone* formed plates, m. p. 222—224°, from ethanol (Found: N, 18·85. $C_{12}H_{19}ON_3$ requires N, 19·0%). Similarly, 4-*iso*propyl*cyclo*hexanone gave the bicyclic

4-iso*propyl homologue* (28%), b. p. 136—139°/18 mm., n_D^{21} 1·5085 (Found: C, 80·9; H, 10·5. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%); its 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 142—144°, from ethanol–ethyl acetate (Found: C, 61·45; H, 6·55; N, 14·9. $C_{19}H_{24}O_4N_4$ requires C, 61·3; H, 6·5; N, 15·0%); light absorption in EtOH: max. at 388 mμ (ε 29,000). 2-Methyl*cyclo*hexanone gave a small yield (9%) of homogeneous bicyclic product, whose 2 : 4-*dinitrophenylhydrazone*, red needles, had m. p. 128—130° (from ethanol–ethyl acetate) (Found: C, 59·5; H, 6·0; N, 16·2. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·8; N, 16·3%) and absorption max. in EtOH 388 mμ (ε 27,900).

Reduction of bicyclo[5 : 3 : 0]*Dec-7-en-9-one.*—(*a*) The unsaturated ketone (90 mg.) in methanol (30 c.c.) was hydrogenated at a palladium–charcoal catalyst (5%; 5 mg.); 14·5 c.c. of hydrogen were taken up in 15 min. at 21°/760 mm. (theor., 14·3 c.c.). The filtered solution was treated with methanolic semicarbazide acetate; the resulting *semicarbazone* crystallised from methanol in needles, m. p. 198—199° (Found: N, 20·0. $C_{11}H_{19}ON_3$ requires N, 20·1%). Heating this semicarbazone with ethanolic 2 : 4-dinitrophenylhydrazine sulphate gave the corresponding 2 : 4-*dinitrophenylhydrazone*, orange-yellow needles, m. p. 125—126°, from ethanol (Found: C, 58·1; H, 6·2; N, 17·0. $C_{16}H_{20}O_4N_4$ requires C, 57·85; H, 6·0; N, 16·85%).

(*b*) A solution of the unsaturated ketone (150 mg.) in ether (5 c.c.) was added to a stirred solution of lithium (100 mg.) in liquid ammonia (50 c.c.). After 30 min. ammonium chloride was added and the ammonia evaporated off. Extraction with ether yielded the saturated ketone, which was converted directly into the semicarbazone, plates, m. p. 221—223° (from ethanol) (Found: N, 19·8%). Treatment of this as described above gave the corresponding 2 : 4-*dinitrophenylhydrazone* which crystallised from ethanol in red sheaves of needles on slow crystallisation or yellow plates on rapid cooling. Both forms partially melted at 129—130°, then rapidly resolidified to a mass of yellow needles which melted sharply at 138° (Found: C, 58·3; H, 6·0; N, 17·0%).

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The Determination of Arrhenius Parameters for a Normal-to-iso-diazoate Transformation.

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The change of the normal sodium diazoate from sulphanilic acid into its *iso*-isomer in aqueous sodium hydroxide is examined kinetically. The results indicate a frequency factor of 10^{13}—10^{14} sec.$^{-1}$ and an energy of activation of 25—27 kcal./mole. This diazoate conversion thus resembles many others, studied previously with molecules containing –N=N– and –N:NO– groups where configurational inversions of *cis*- to *trans*-forms have been involved.

So far, the possibilities of geometrical isomerism with molecules generalisable as X·N:N·Y have been considered by Le Fèvre and his collaborators for the cases (*a*) where X = an aryl or substituted aryl group and Y is one of the following radicals: Ph (*J.*, 1939, 531; 1948, 1949; 1949, 1595; 1952, 4082; 1953, 867), –CN (*J.*, 1938, 431, 1878; 1947, 445, 457; 1949, 333, 944, 1106; 1950, 185, 3128), $-SO_2\cdot O\cdot$Metal (*J.*, 1951, 415), $-SO_2\cdot$Aryl (*J.*, 1952, 3381), $-CO\cdot NH_2$ (*J.*, 1951, 1977), –NHAr (*J.*, 1951, 2743; 1952, 2932), or (*b*) where X = Y = *p*-$HO\cdot C_6H_4$– (*J.*, 1939, 535), or (*c*) where X = Y = C_5H_4N– (*J.*, 1951, 1814; compare Campbell, Henderson, and Taylor, *J.*, 1953, 1281). Observations relevant to examples contained in (*a*)—(*c*) are also given in *Chem. and Ind.*, 1948, 158, 543, 732, 782; 1953, 378; and in *Austral. J. Chem.*, 1953, **6**, 341. Conclusions, in general, have been reconcilable with Hantzsch's stereochemical concept (*Ber.*, 1894, **27**, 1702) that the –N=N– unit can exist in a *cis*- or *trans*-configuration.

The objective of the present work was to supplement the above by a kinetic study of

the transformation of a normal to an *iso*diazoate, in which X = aryl or substituted aryl and Y (following Hantzsch's proposal) may be –O·Metal. At first sight the conditions necessary to bring about this change appear against the simple idea that it is geometric, for whereas diazocyanides, diazosulphonates, azobenzene, and various other azo-derivatives undergo interconversion spontaneously in non-polar solvents at low temperatures, the *n*-diazoates are often subjected to very concentrated alkalis at 100° or more during the preparations of their *iso*-forms. Less drastic treatment sometimes increases unwanted side-reactions. Jolles and Camiglieri (*Gazzetta*, 1932, **62**, 720) have reported that at 25° in 0·4N-aqueous sodium hydroxide the percentage conversions for the diazoates from aniline, *m*-toluidine, and *o*-anisidine are only 12—15, while from *p*-toluidine, *p*-phenetidine, and *p*-anisidine the yields are " traces," the rest being tar; Oddo, Indovina, Albanese, and Amatore (*ibid.*, 1935, **65**, 939), by examining 24 diazoates, including those from the *o*-, *m*-, and *p*-halogenoanilines, -nitroanilines, and -anisidines, have concluded that, in general, increased alkalinity decreases decomposition and raises the amount of *iso*diazoate obtained. The last group of authors utilised 0·4, 0·8, and 1·6% solutions of sodium hydroxide and estimated the nitrogen evolution, resin production, and quantity of *iso*diazoate formed in each case. The maximum yields of *iso*diazoates were of the order 75%, and always accompanied by considerable decomposition.

Our preliminary experiments confirmed the extensive decomposition suffered by most normal diazoates when treated with aqueous alkalis of a convenient concentration, *i.e.*, one at which the reaction mixture remained homogeneous during the change. We noticed, however, that Brown, Duffin, Maynard, and Ridd (*J.*, 1953, 3936), while tabulating quantitative data concerning the coupling of diazotised sulphanilic acid with glyoxaline, indicate that decomposition of the diazonium compound increases with pH until pH 10, after which one observation at pH 11 suggests that it decreases. (The " decomposition," whose first-order coefficients were around 10^{-5} sec.$^{-1}$, was estimated by coupling; this does not differentiate between actual decomposition and change into *iso*diazoate.) We confirmed this and ascertained that the sodium diazoate from sulphanilic acid undergoes 97—100% conversion into the *iso*diazoate in sodium hydroxide solutions ranging from 0·5 to 4·85N. It thus fulfilled our requirements.

Experimental

Sulphanilic acid was diazotised to give the solid diazobenzene-*p*-sulphonic acid. This was stirred with an equal weight of crushed ice, and 50% aqueous sodium hydroxide added gradually until a clear lemon-yellow solution was obtained. The latter, on cooling and treatment with more alkali, deposited crystals of the normal diazoate. A quantitative yield was obtainable by precipitation below 0° with 95% alcohol. The crystals were filtered by suction in air free from carbon dioxide, washed with cold alcohol, and dried *in vacuo*.

Solutions for the kinetic observations were made up in the range 0·0015—0·0036M with respect to the normal diazoate. A weighed quantity of the last-named was added to the sodium hydroxide solution (of appropriate concentration) which had been previously in a thermostat for some time. A further period was allowed for attainment of thermal equilibrium before measurements were begun. Samples (1 ml.) were then extracted and coupled with a slightly alkaline solution of β-naphthol. The Beer–Lambert law was found to hold under these conditions, colour being estimated by a Hilger Spekker photoelectric absorptiometer, a blue filter (Ilford 602) being used. The velocity constant was obtained from the slope of the graph $\log (E_0-E_\infty)/(E_t-E_\infty)$ against time, where E_0 and E_∞ are the readings at the beginning and end of the experiments. Least-square methods gave essentially the same values of the velocity constant. The slopes of the straight lines so obtained for various concentrations of diazoate yielded constant values of k, indicating the applicability of first-order kinetics. This is the case for the total rate of change. It was established, by acidifying and coupling samples at the beginning and at the close of the experiments, that conversion was nearly quantitative (97—100%) for all strengths of alkali given in the Table. The values of k were therefore assumed to be those for the change of normal to *iso*-diazoate in the various media.

Results are set out in Table 1 which also includes the derived A and E terms of the Arrhenius equation.

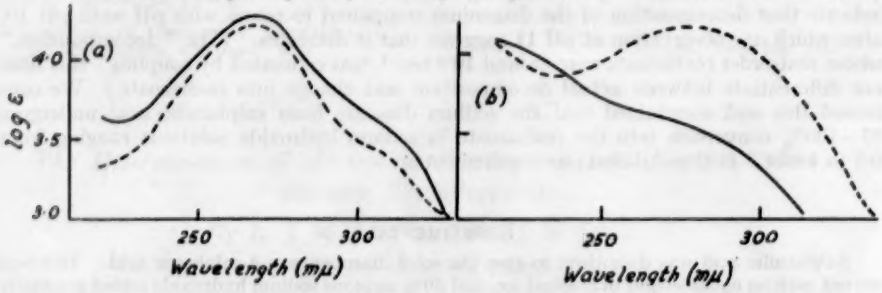
TABLE 1. *Conversion of normal into* iso-NaO·SO_2·C_6H_4·N_2·ONa.

Temp.	10^4k (sec.$^{-1}$)	E (kcal./mole)	$10^{-13}A$ (sec.$^{-1}$)	Temp.	10^4k (sec.$^{-1}$)	E (kcal./mole)	$10^{-13}A$ (sec.$^{-1}$)
	NaOH; 0·501N				NaOH; 2·2N		
40°	0·32	26·1	7·9	40°	0·2715	26·4	$8·4_5$
50	1·57			50	1·395		
60	4·87			60	4·483		
65	8·10			65	7·082		
	NaOH; 1·292N				NaOH; 4·85N		
40	0·329, 0·320	25·4	2·1	40	1·1462	25·0	2·0
50	1·330, 1·300			50	1·469		
60	3·63, 3·59			60	6·32		
64·5	6·774			65	10·33		
	NaOH; 1·3N						
40	0·2967	25·7	4·1				
50	1·279						
60	3·761						
65	7·56						

DISCUSSION

The frequency factors and energies of activation (*viz.*, 10^{13}—10^{14}, and 25—27 kcal./mole) now ascertained for a normal→*iso*-diazoate change are similar to those previously reported for various inversions about the azo- and azoxy-groupings (see Table 2 for summary and references). They resemble also the values recorded for the transform-

Ultraviolet absorption spectra of diazoates from sulphanilic acid. —— Normal; - - - *iso.*



ation of *cis*- into *trans*-piperonaldoximes (namely, 10^{13}—10^{15}, and 22—27 kcal./mole; Le Fèvre and Northcott, *J.*, 1949, 2235) but differ somewhat from the figures found for the interconversion of the stilbenes (10^{10}, and 36·7 kcal./mole; Taylor and Murray, *J.*, 1939, 2078). There is nothing here against the existence of a common mechanism for all cases where the double bond involves at least one nitrogen atom. A point of interest now revealed is the smallness of the effect on the kinetics of varying the medium from aqueous alkali through polar to non-polar liquids or the solute from the electrovalent diazoates to the covalent azo- and azoxy-benzenes. By analogy therefore our belief is strengthened that the isomerisation of normal diazoates is geometrical in nature and essentially concerns the anions.

Absorption Spectra of the Isomeric Sodium Diazoates from Sulphanilic Acid.—In aqueous solutions both forms absorb strongly and similarly at 270 mμ (log ε 4·2); the log ε–wavelength plots indicate that the absorptions are more intense below 200 mμ. Minima occur at 225 mμ. Rather broad shoulders are found between *ca.* 290 (log ε 3·8) and *ca.* 320 mμ (log ε 3·2). The spectra (Fig., *a*) are otherwise featureless, and in general shape reminiscent of that for *N*-methyl-*N*-nitrosoaniline in alcohol ($\lambda_{max.}$ 275 mμ, log ε 3·9; Earl, Le Fèvre, and Wilson, *J.*, 1949, S 103). These results differ somewhat where relative intensities are concerned from those secured in dilute aqueous sodium hydroxide by Hantzsch and Lifschitz (*Ber.*, 1912, **45**, 3029) whose graph indicated that at *ca.* 286 mμ the "*anti*" salt exhibited a maximum absorption while the "*syn*" salt absorbed less strongly and displayed

a very broad inflexion. Repetition, however, in 0·1N-sodium hydroxide solution (Fig., *b*) confirms Hantzsch and Lifschitz's findings.

We mention specifically that the coupling powers of our solutions were checked by experiment, and that the contrast in this ability was retained after the determinations of absorption were completed.

TABLE 2. *Summary of previous kinetic studies involving geometrical change about the* −N=N− *group.*

cis-to-*trans*-Change	Solvent	*A*	*E* (kcal./mole)	Reference
p-Br·C_6H_4·N:N·CN	C_6H_6	*ca.* 10^{13}	*ca.* 22	Le Fèvre and Vine, *J.*, 1938, 431
α- and β-$C_{10}H_7$·N:N·CN	C_6H_6	10^{13}	23	Le Fèvre and Northcott, *J.*, 1949, 333
p-Cl·C_6H_4·N:N·CN	8 various	10^{11}—10^{15}	21—26	*Idem, ibid.*, p. 944
p-X·C_6H_4·N:N·CN (X = H, Me, Cl, Br, NO_2, and MeO) and 2 : 4 : 6-$Br_3C_6H_2$·N:N·CN	C_6H_6	10^{11}—10^{15}	21—26	,, ,,
C_6H_5·C_6H_4·N:N·CN	C_6H_6	10^{11}	22	Freeman and Le Fèvre, *J.*, 1950, 3128
4′-Br·C_6H_4·C_6H_4·N:N CN	C_6H_6	10^{12}	21·5	,, ,,
C_6H_5·N:N·C_6H_5	16 various	10^{13}—10^{14}	22—25	Halpern, Brady, and Winkler, *Canad. J. Res.*, 1950, **28**, *B*. 140
C_6H_5·N:N(O)·C_6H_5	9 various	10^{13}—10^{15}	22—25	Luner and Winkler, *Canad. J. Chem.*, 1952, **30**, 679
4 : 4′-Me·C_6H_4·N:N(O)·C_6H_4Me	,,	10^{13}—10^{15}	22—24	,, ,, ,,
C_6H_5·N:N·C_6H_5	7 various	10^{10}—10^{13}	22—28	Le Fèvre and Northcott, *J.*, 1953, 867
p-X·C_6H_4·N:N·C_6H_5 (X = Me, Cl, Br, NO_2, and MeO)	C_6H_6	10^{10}—10^{12}	22—25	,, ,, ,,

Nujol mulls of the solid isomers used in the above kinetic study give infrared spectra having dissimilarities. Table 3 lists the bands recorded together with—for comparison—those from sodium sulphanilate.

TABLE 3. *Infrared absorptions.*

Normal diazoate	*iso*-Diazoate	Na sulphanilate	Assignment	Normal diazoate	*iso*-Diazoate	Na sulphanilate	Assignment
3630 (w)		—	Combined H_2O	1195 (s, broad)	1195 (s, broad)	1173 (ms)	C–H rocking
		3463 (s)	N–H				
1923	1918 (w)	1900 (w)		1132 (m)	1132 (m)	1120 (ms)	C–N
	1692 (w)	1654 (m)		1107 (w)	1107 (m)		See text
1622		1625 (m)	Combined H_2O	1034	1045	1033 (ms)	ν_{14} of benzene
	1599	1599 (m)		1009	1010 (w)	1000 (ms)	$(SO_3{\cdot}O)^-$
	1580 (w)					947 (w)	
		1503 (w)		917	917		See text
	1417 (w)	1457 (w)		842	845	835 (s)	*p*-Disubstd. benzene
		1436 (w)					
		1376 (m)		823 (w)			
1307 (w)	1302 (w)	1302 (ms)	C–N	786			
1284 (w)		1282 (ms)		750	756	721	Ar ring
		1237 (ms)	$(SO_3{\cdot}O)^-$?			697 (s)	

It is seen that only two absorptions are common to the isomeric diazoates and absent from sodium sulphanilate, *viz.*, those at 1107 and 917 cm.$^{-1}$. When this is considered in conjunction with the bands found for other diazo-derivatives (Le Fèvre, O'Dwyer, and Werner, *Austral. J. Chem.*, 1953, **6**, 341) the 1107-cm.$^{-1}$ band did not appear with the labile potassium benzene diazoate. It is unlikely therefore to be the N–O$^-$ frequency which we were hoping to reveal. The feature at 917 cm.$^{-1}$ likewise cannot be due to N–O$^-$ since all azo-compounds, including diazoates, examined to date, absorb near this point (*cis*- and *trans*-azobenzenes, 918 and 923 cm.$^{-1}$; diazosulphonates, *ca.* 960 cm.$^{-1}$; diazosulphones, 880—944 cm.$^{-1}$; azopyridine, 960 cm.$^{-1}$; azomethane, 932 cm.$^{-1}$; 1-methyl-1 : 2 : 3-benzotriazole, 936 cm.$^{-1}$; cf. Le Fèvre, O'Dwyer, and Werner, *loc. cit.*).

Tetlow (*Research*, **1950**, **3**, 187) ascribes the band (recorded by him at 927 cm.$^{-1}$) in the azobenzenes to the fragment C–N=N–C, but its emergence in diazoates and the triazole must limit this suggestion to C–N=N–X, where X is not a carbon atom.

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4-*Alkyl*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine Derivatives.*

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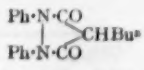
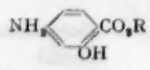
Condensations of 4 : 4′-diethoxycarbonylhydrazobenzene with alkylmalonyl chlorides give 4-alkyl-3 : 5-dioxo-1 : 2-di-*p*-ethoxycarbonylphenylpyrazolidines which on hydrolysis yield the corresponding carboxylic acids. Oxidation of methyl 4-aminosalicylate by sodium perborate yields 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene reduction of which gives the hydrazobenzene. Acetylation of the latter, followed by condensation with alkylmalonyl chlorides and hydrolysis, gives the corresponding 4-alkyl-3 : 5-dioxo-1 : 2-di-(4-carboxy-3-hydroxyphenyl)pyrazolidines.

Although phenylbutazone (4-*n*-butyl-3 : 5-dioxo-1 : 2-diphenylpyrazolidine) (I) is of value in the treatment of rheumatoid arthritis and allied conditions, indications of toxic effects associated with its use have been reported (Leonard, *Brit. Med. J.*, **1953**, I, 1311; Benstead, *ibid.*, p. 711; Johnson and Larkin, *ibid.*, **1954**, II, 1088; Etess and Jacobson, *J. Amer. Med. Assoc.*, **1953**, **151**, 639; Hinz, Lamont-Havers, Cominsky, and Gaines, *ibid.*, p. 38; Kiely and Stickney, *Proc. Mayo Clin.*, **1953**, **28**, 341). Since it is possible that *in vivo*



(I)



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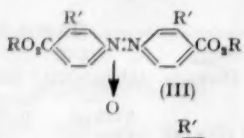

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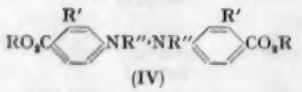

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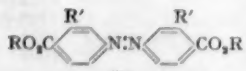

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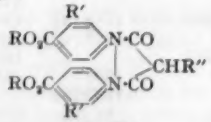

(VI)

phenylbutazone may in part be degraded to hydrazobenzene, the toxic hazards associated with phenylbutazone may be attributable to hydrazobenzene. On this working hypothesis, the present investigation aimed at replacing the hydrazobenzene moiety in phenylbutazone by a related compound relatively free from toxic hazard. Although aniline, which we assume to be the parent of hydrazobenzene, is a systemic poison, the related *p*-aminobenzoic acid and 4-aminosalicylic acid (II; R = H) are relatively non-toxic. This paper describes the preparation of a series of 4-alkyl-3 : 5-dioxo-1 : 2-di-*p*-carboxyphenylpyrazolidines (VI; R = R′ = H, R″ = alkyl) and of a related series of hydroxy-derivatives (VI; R = H, R′ = OH, R″ = alkyl); the pharmacology of these compounds will be reported elsewhere.

Two practical methods for the preparation of 3 : 5-dioxopyrazolidines consist in (*a*) heating a malonic ester with hydrazobenzene and sodium alkoxide at 150—200° (Ruhkopf, *Ber.*, **1940**, **73**, 820), and (*b*) reaction of a malonyl chloride with hydrazobenzene alone (Tsumaki, *Bull. Soc. Chem. Japan*, **1931**, **6**, 1) or in the presence of pyridine at 0° (B.P.

646,597). Condensation of 4 : 4′-diethoxycarbonylhydrazobenzene with a number of malonic esters (method *a*) failed to give the desired product, extensive decomposition occurring. The use of alkylmalonyl chlorides in ether–pyridine gave the 3 : 5-dioxopyrazolidines in moderate yield. Use of chloroform–pyridine gave improved yields, probably owing to the greater solubility of the alkylmalonyl chloride–pyridine complex in chloroform. The yields also increased with the size of the alkyl group. Alkaline hydrolysis of the 3 : 5-dioxopyrazolidine esters (VI; R = Et, R′ = H, R″ = alkyl) gave the required acids, the properties of which are summarised in Table 1.

Oxidation of methyl 4-aminosalicylate (II; R = Me) by a modification of the sodium perborate method (Mehta and Vakilwala, *J. Amer. Chem. Soc.*, 1952, **74**, 563) gave 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (III; R = Me, R′ = OH). In contrast, ethyl 4-aminobenzoate and the amines used by the Indian authors gave azo-derivatives under the same conditions. We find that oxidation of methyl and ethyl 4-aminosalicylates with hydrogen peroxide in acetic acid gives the azoxy-compounds (III; R = Me and Et respectively, R′ = OH). Reduction of 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (III; R = Me, R′ = OH) with zinc dust and acetic acid gave the hydrazo-compound (IV; R = Me, R′ = OH, R″ = H) which was oxidised by sodium perborate to the azo-derivative (V; R = Me, R′ = OH); the latter is reconverted into the hydrazo-compound by zinc dust and acetic acid. These azoxy-, hydrazo-, and azo-esters have been characterised by diacetyl and dibenzoyl derivatives. Zinc and acetic acid reduced the dibenzoyloxyazoxy-compound (III; R = Me, R′ = OBz) or the dibenzoyloxyazo-analogue (V; R = Me, R′ = OBz) to the dibenzoyloxyhydrazo-compound (IV; R = Me, R′ = OBz, R″ = H) and, conversely, oxidation of the last product with sodium perborate gave the dibenzoyloxyazo-compound (V; R = Me, R′ = OBz). Hydrolysis of the azoxy-, hydrazo-, and azo-esters gave the corresponding acids. Vigorous benzoylation of the dihydroxyhydrazo-ester (IV; R = Me, R′ = OH, R″ = H) gave the tetrabenzoyl derivative (IV; R = Me, R′ = OBz, R″ = Bz).

Treatment of 3 : 3′-diacetoxy-4 : 4′-dimethoxycarbonylhydrazobenzene (IV; R = Me, R′ = OAc, R″ = H) with an alkylmalonyl chloride in pyridine–ether, followed by extraction of the product with aqueous potassium hydroxide, gave the 4-alkyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidine (VI; R = Me, R′ = OH, R″ = alkyl). When *n*-butylmalonyl chloride was used, however, the product was also isolated by extraction with aqueous sodium carbonate and 1 : 2-di-(3-acetoxy-4-methoxycarbonylphenyl)-4-*n*-butyl-3 : 5-dioxopyrazolidine (VI; R = Me, R′ = OAc, R″ = Bu^n) was obtained; it was identical with the acetylation product of the phenol (VI; R = Me, R′ = OH, R″ = Bu^n). Lower yields were obtained by reaction of the alkylmalonyl chloride with the hydrazo-compound in pyridine–chloroform, possibly because of emulsion formation during the alkali extraction and the consequent longer exposure of the products to alkali. Hydrolysis of the hydroxy-esters (VI; R = Me, R′ = OH, R″ = alkyl) gave the corresponding, desired acids (see Table 2).

Experimental

4 : 4′-*Diethoxycarbonylazoxybenzene* (III; R = Et, R′ = H).—4 : 4′-Dicarboxyazoxybenzene (103·5 g.) (Galbraith, Degering, and Hitch, *J. Amer. Chem. Soc.*, 1951, **73**, 1323) and thionyl chloride (250 c.c.) were refluxed for 6 hr. Excess of thionyl chloride was removed under reduced pressure, the crude acid chloride in dry benzene (200 c.c.) was treated with ethanol (80 c.c.), and the mixture refluxed for 30 min. The filtered solution was evaporated and the residue crystallised from ethanol (250 c.c.). The azoxy-ester (103 g., 82%) separated as salmon-pink plates, m. p. 110—112°. Meyer and Dahlem (*Annalen*, 1903, **326**, 334) describe this ester, which they obtained *via* the silver salt, as yellow needles (from ethanol), m. p. 114·5°.

4 : 4′-*Diethoxycarbonylhydrazobenzene* (IV; R = Et, R′ = R″ = H).—The azoxy-ester (III; R = Et, R′ = H) (114·5 g.) in hot glacial acetic acid (500 c.c.) was treated portionwise with zinc dust (100 g.) with stirring. The hot mixture was filtered and the filtrate diluted with water (500 c.c.). The hydrazo-compound (97·5 g., 89%) separated as needles, m. p. 117·5—119°. Meyer and Dahlem (*loc. cit.*) give m. p. 118°.

3 : 3′-*Dihydroxy*-4 : 4′-*dimethoxycarbonylazoxybenzene* (III; R = Me, R′ = OH).—(*a*) A solution of methyl 4-aminosalicylate (4·0 g.) in glacial acetic acid (100 c.c.) was treated with 54% sodium perborate (7·3 g.) at room temperature with shaking. Next morning the solid was collected, washed with water, and crystallised from ethyl acetate from which **3 : 3′-*dihydroxy*-4 : 4′-*dimethoxycarbonylazoxybenzene*** (1·3 g.) separated as red needles, m. p. 193—194° (Found: C, 55·8; H, 4·0. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1%).

(*b*) Methyl 4-aminosalicylate (80 g.) in warm acetic acid (650 c.c.) was treated with hydrogen peroxide (450 c.c.; 30%) and kept at room temperature for 72 hr. Crystallisation of the separated solid (41 g.) from glacial acetic acid gave the azoxy-compound as orange-red needles, m. p. and mixed m. p. 193—194° (Found: C, 55·8; H, 4·0; N, 8·15. $C_{16}H_{14}O_7N_2$ requires N, 8·1%).

The *diacetyl* derivative (III; R = Me, R′ = OAc), prepared by the action of acetic anhydride–pyridine at room temperature followed by isolation using ether, separated from methanol as orange needles, m. p. 123—124° (Found: C, 56·2; H, 4·2. $C_{20}H_{18}O_9N_2$ requires C, 55·8; H, 4·2%).

The *dibenzoyl* derivative (III; R = Me, R′ = OBz) was prepared by treating a solution of 3 : 3′-dihydroxy-compound (1·0 g.) in pyridine (40 c.c.), at 30°, with benzoyl chloride (5 c.c.). Next morning the product was precipitated by adding water and crystallised from glacial acetic acid, from which it forms yellow blades, m. p. 187—188° (Found: C, 65·2; H, 4·5. $C_{30}H_{22}O_9N_2$ requires C, 65·0; H, 4·0%).

By using the hydrogen peroxide–acetic acid method **4 : 4′-*diethoxycarbonyl*-3 : 3′-*dihydroxy*-*azoxybenzene*** (III; R = Et, R′ = OH) was prepared from ethyl 4-aminosalicylate. It formed orange needles or red prisms (from ethanol), m. p. 137° (Found: C, 57·9; H, 5·0; N, 7·7. $C_{18}H_{18}O_7N_2$ requires C, 57·75; H, 4·85; N, 7·5%).

4 : 4′-*Dicarboxy*-3 : 3′-*dihydroxyazoxybenzene* (III; R = H, R′ = OH).—**3 : 3′**-Dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (0·5 g.) was refluxed with 10% aqueous potassium hydroxide (25 c.c.) for 1 hr. The cooled solution was acidified (Congo-red) with dilute hydrochloric acid, and the precipitate collected and washed with water: purification by extraction with hot acetone (100 c.c.), filtration, and concentration of the filtrate to *ca.* 10 c.c. gave the *acid* as a brown powder, decomp. above 300° (Found: C, 52·4; H, 3·4. $C_{14}H_{10}O_7N_2$ requires C, 52·8; H, 3·2%).

3 : 3′-*Dihydroxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OH, R″ = H).—A solution of **3 : 3′**-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (4·0 g.) in glacial acetic acid (50 c.c.) was heated on the steam-bath for 30 min. with zinc dust (8·0 g.). The filtered mixture was treated with water, and the solid collected and crystallised from glacial acetic acid from which **3 : 3′-*dihydroxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (2·6 g.) forms needles, m. p. 198—199° (Found: C, 58·0; H, 4·75. $C_{16}H_{16}O_6N_2$ requires C, 57·8; H, 4·85%). This compound (m. p. and mixed m. p. 198—199°) is also obtained by zinc and acetic acid reduction of 3 : 3′-dihydroxy-4 : 4′ dimethoxycarbonylazobenzene.

Similar zinc and acetic acid reduction of 4 : 4′-diethoxycarbonyl-3 : 3′-dihydroxyazobenzene gave **4 : 4′-*diethoxycarbonyl*-3 : 3′-*dihydroxyhydrazobenzene*** (IV; R = Et, R′ = OH, R″ = H) which separates from aqueous ethanol as needles, m. p. 150—151° (Found: C, 59·8; H, 5·7; N, 7·5. $C_{18}H_{20}O_6N_2$ requires C, 60·0; H, 5·6; N, 7·8%).

3 : 3′-*Diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OAc, R″ = H).—A solution of the hydrazo-compound (IV; R = Me, R′ = OH, R″ = H) (10 g.) in pyridine (60 c.c.) and acetic anhydride (60 c.c.) was kept overnight in nitrogen at room temperature. Isolation by means of ether gave **3 : 3′-*diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (IV; R = Me, R′ = OAc, R″ = H) (12·3 g.) which separates from methanol as pink rosettes of small needles, m. p. 156—158° (Found: C, 57·8; H, 4·7. $C_{20}H_{20}O_8N_2$ requires C, 57·7; H, 4·8%).

3 : 3′-*Dibenzoyloxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OBz, R″ = H).—(*a*) Treatment of the hydroxy-hydrazo-ester (IV; R = Me, R′ = OH, R″ = H) with 2 mols. of benzoyl chloride in pyridine at room temperature overnight was followed by isolation using ether. The dried ethereal solution was shaken with activated zinc and then evaporated, to give **3 : 3′-*dibenzoyloxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (46%) as plates, m. p. 220—221°, from glacial acetic acid (Found: C, 66·6; H, 4·4. $C_{30}H_{24}O_8N_2$ requires C, 66·7; H, 4·5%).

(*b*) Reduction of either **3 : 3′**-dibenzoyloxy-4 : 4′-dimethoxycarbonyl-azoxybenzene (III; R = Me, R′ = OBz), or -azobenzene (V; R = Me, R′ = OBz) with zinc dust and acetic acid at 90° gave, in good yield, **3 : 3′**-dibenzoyloxy-4 : 4′-dimethoxycarbonylhydrazobenzene which separates from glacial acetic acid as plates, m. p. and mixed m. p. 219—220°.

NN'-*Dibenzoyl*-3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R' = R'' = OBz).—The hydroxy-hydrazo-ester (IV; R = Me, R' = OH, R'' = H) (3·0 g.) in pyridine (30 c.c.) was heated with benzoyl chloride (10 c.c.) on the steam-bath for 2 hr. The mixture was worked up with ether. On standing, the ether solution deposited 3 : 3'-dibenzoyloxy-4 : 4'-dimethoxycarbonylazobenzene (0·3 g.), m. p. 201—203° undepressed on admixture with an authentic specimen (see below). Removal of the ether gave a red gum which crystallised from methanol. Recrystallisation from glacial acetic acid gave NN'-*dibenzoyl*-3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylhydrazobenzene* (1·2 g.) as plates, m. p. 180—181° (Found : C, 70·8; H, 4·4. $C_{44}H_{32}O_{10}N_2$ requires C, 70·6; H, 4·3%).

4 : 4'-*Dicarboxy*-3 : 3'-*dihydroxyhydrazobenzene* (IV; R = R'' = H, R' = OH).—(*a*) hydrolysis of the hydroxy-hydrazo-ester (IV; R = Me, R' = OH, R'' = H) with alkali, followed by purification of the product by dissolution in pyridine and precipitation with dilute hydrochloric acid, gave the *acid* as a cream-coloured amorphous solid, m. p. 206—207° (Found : C, 56·1; H, 3·8. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0%).

(*b*) 4-Nitrosalicylic acid (3·65 g.) in 5N-sodium hydroxide (20 c.c.) was treated on the steam-bath during 1½ hr. with zinc dust (8·0 g.). The filtered mixture was acidified (Congo-red) with dilute hydrochloric acid, and the precipitate digested with hot ethanol and further treated as above, to give the acid, m. p. and mixed m. p. 205° (Found : C, 55·2; H, 3·5%).

3 : 3'-*Dihydroxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OH).—A hot solution of 3 : 3'-dihydroxy-4 : 4'-dimethoxycarbonylhydrazobenzene (0·5 g.) in glacial acetic acid (15 c.c.) was treated with 54% sodium perborate (0·25 g.). After cooling, the red solid was collected and crystallised from ethyl acetate from which 3 : 3'-*dihydroxy*-4 : 4'-*dimethoxycarbonylazobenzene* (400 mg.) separated as bright red needles, m. p. 214—216° (Found : C, 58·4; H, 4·2. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3%).

3 : 3'-*Diacetoxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OAc).—(*a*) 3 : 3'-Diacetoxy-4 : 4'-dimethoxycarbonylhydrazobenzene (0·5 g.) in warm glacial acetic acid (20 c.c.) was heated with 54% sodium perborate (0·2 g.) on the steam-bath for 15 min. The cooled mixture was filtered and the solid crystallised from chloroform–methanol, from which 3 : 3'-*diacetoxy*-4 : 4'-*dimethoxycarbonylazobenzene* (400 mg.) separated as red prismatic plates, m. p. 179—181° (Found : C, 58·4; H, 4·6. $C_{20}H_{18}O_8N_2$ requires C, 58·0; H, 4·4%).

(*b*) Acetylation of 3 : 3'-dihydroxy-4 : 4'-dimethoxycarbonylazobenzene (1·0 g.) with acetic anhydride (6 c.c.) and pyridine (6 c.c.) on the steam-bath for 1 hr., followed by isolation using ether, gave the diacetate (1·0 g.) as light red prisms, m. p. and mixed m. p. 178—180°, from ethyl acetate–light petroleum (b. p. 60—80°) (Found : C, 58·4; H, 4·3%).

3 : 3'-*Dibenzoyloxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OBz).—(*a*) Oxidation of 3 : 3'-dibenzoyloxy-4 : 4'-dimethoxycarbonylhydrazobenzene with sodium perborate in glacial acetic acid gave 3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylazobenzene* which separates from ethyl acetate as orange needles, m. p. 208—209° (Found : C, 67·0; H, 3·8. $C_{30}H_{22}O_8N_2$ requires C, 66·9; H, 4·1%).

(*b*) Treatment of the hydroxy-azo-ester (V; R = Me, R' = OH) with benzoyl chloride and pyridine on the steam-bath for 30 min. gave the dibenzoate (V; R = Me, R' = OBz) as orange needles, m. p. and mixed m. p. 208—209°.

4 : 4'-*Dicarboxy*-3 : 3'-*dihydroxyazobenzene* (V; R = H, R' = OH).—3 : 3'-Dihydroxy-4 : 4'-dimethoxycarbonylazobenzene was hydrolysed by alkali. The amorphous red *acid* which decomposed at *ca.* 290° was purified by digestion with hot acetone (Found : C, 54·6; H, 3·4. $C_{14}H_{10}O_6N_2$ requires C, 55·6; H, 3·3%).

Condensations of 4 : 4'-*Diethoxycarbonylhydrazobenzene with Alkylmalonyl Chlorides.*—The alkylmalonyl chlorides were prepared by alkylation of ethyl malonate (*Org. Synth.*, Coll. Vol. I, 2nd. edn., p. 250; Coll. Vol. II, p. 279), and hydrolysis of the resulting esters to the malonic acids (cf. *Org. Synth.*, Coll. Vol. II, p. 93). These were refluxed for 2 hr. with thionyl chloride, the excess of reagent was removed, and the residue distilled under reduced pressure. n-*Hexylmalonyl chloride* has b. p. 124°/16 mm. (Found : Cl, 32·6. $C_9H_{14}O_2Cl_2$ requires Cl, 31·5%).

The acid chloride (0·17 mole) was added dropwise to a stirred solution of dry pyridine (85 c.c.) in dry chloroform (100 c.c.) at −10°. 4 : 4'-Diethoxycarbonylhydrazobenzene (50 g.) in chloroform (500 c.c.) was added with stirring at 0° and the mixture allowed to attain room temperature. After 12 hr., the mixture was washed with 2N-hydrochloric acid, water, and 2N-sodium carbonate. Acidification of the alkaline extracts and crystallisation of the product gave the 4-*alkyl*-3 : 5-*dioxo*-1 : 2-*di*-p-*ethoxycarbonylphenylpyrazolidine* (Table 1; yields, 40—80%).

Hydrolysis.—The diethyl esters (10 g.) were hydrolysed by refluxing N-sodium hydroxide

(100 c.c.) for 45 min. Acidification with dilute hydrochloric acid liberated the acids (see Table 1; yields, 70—80%).

Condensations of 3 : 3′-*Diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene with Alkylmalonyl Chlorides.*—The acid chloride (0·018 mole) in dry ether (30 c.c.) was added dropwise to a stirred mixture of pyridine (20 c.c.) and dry ether (20 c.c.) at −15°. The suspension was then treated with a solution of 3 : 3′-diacetoxy-4 : 4′-dimethoxycarbonylhydrazobenzene (0·012 mole) in pyridine–ether (80 c.c.; 1 : 1) during 45 min. at −15°. Stirring was continued for 30 min. at −15°; the cooling-bath was then removed and stirring continued for 3 hr. The mixture was diluted with ether (100 c.c.) and washed with excess of 5% hydrochloric acid. The ether was extracted with 2% aqueous potassium hydroxide (3 × 50 c.c.), and the extracts were washed with ether and acidified (Congo-red) with 5% hydrochloric acid. The crude 4-alkyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidines were purified by crystallisation (Table 2; yields: 30—50%). The hydroxy-esters gave a purple colour with aqueous-ethanolic ferric chloride.

TABLE 1. 3 : 5-*Dioxopyrazolidines* (VI; R′ = H).

Substituent					Found (%)				Required (%)		
R	R″	M. p.	Solvent †	Form	C	H	N	Formula	C	H	N
Et	Et	200—201°	EtOH	Prisms	65·0	5·9	6·3	$C_{23}H_{24}O_6N_2$	65·1	5·7	6·6
H	Et	270—280 (decomp.)	Aq. MeOH	Micro-cryst.	62·0	4·5	7·9	$C_{19}H_{16}O_6N_2$	61·9	4·4	7·6
Et	Pr^n	198—200	EtOH	Prismatic needles	65·9	6·0	6·0	$C_{24}H_{26}O_6N_2$	65·7	6·0	6·4
H	Pr^n	228—229 (decomp.)	EtOAc	Prisms	62·5	5·0	7·4	$C_{20}H_{18}O_6N_2$	62·8	4·75	7·3
Et	Pr^i	180	EtOH	Needles	65·8	6·0	6·4	$C_{24}H_{26}O_6N_2$	65·7	6·0	6·4
H	Pr^i	275 (decomp.)	EtOAc–Pet	Rhombs	62·95	4·7	7·3	$C_{20}H_{18}O_6N_2$	62·8	4·75	7·3
Et	Bu^n	158—159	EtOH	Needles	65·9	6·2	—	$C_{25}H_{28}O_6N_2$	66·4	6·2	—
H *	Bu^n	222—224 (decomp.)	EtOAc–Pet	Needles	—	—	7·0	$C_{21}H_{20}O_6N_2$	—	—	7·1
Et	*n*-C_6H_{13}	132—133	EtOH	Needles	68·0	5·8	—	$C_{27}H_{32}O_6N_2$	67·5	6·7	—
H	*n*-C_6H_{13}	245 (decomp.)	EtOH	Needles	64·3	5·8	6·45	$C_{23}H_{24}O_6N_2$	65·1	5·7	6·6

* Crystallisation from 50% aqueous ethanol yielded the *hemihydrate* as needles, m. p. 209—210° (Found: C, 62·0; H, 5·3; N, 6·75. $C_{21}H_{20}O_6N_2,\frac{1}{2}H_2O$ requires C, 62·2; H, 5·2; N, 6·9%).

† Pet = light petroleum (b. p. 60—80°).

TABLE 2. 3 : 5-*Dioxopyrazolidines* (VI; R′ = OH).

Substituent					Found (%)			Required (%)	
R	R″	M. p.	Solvent *	Form	C	H	Formula	C	H
Me	Me	283—284°	AcOH	Prismatic needles	57·8	4·5	$C_{20}H_{18}O_6N_2$	58·0	4·4
H	Me	272—273 †	MeOH–H_2O	Micro-cryst.	56·0	3·6	$C_{19}H_{16}O_6N_2$	56·0	3·7
Me	Et	244—246	$CHCl_3$–MeOH	Prisms	58·7	4·6	$C_{21}H_{20}O_6N_2$	58·9	4·7
H	Et	280—282 †	Et_2O–Pet	Square plates	57·4	4·1	$C_{19}H_{16}O_6N_2$	57·0	4·0
Me	Pr^n	164	$CHCl_3$–MeOH	Prismatic needles	59·7	4·7	$C_{22}H_{22}O_6N_2$	59·7	5·0
H	Pr^n	256 †	AcOH	Prisms	58·3	4·8	$C_{20}H_{18}O_6N_2$	58·0	4·4
Me	Pr^i	186—187	$CHCl_3$–MeOH	Prismatic needles	60·0	5·0	$C_{22}H_{22}O_6N_2$	59·7	5·0
H	Pr^i	270 †	EtOH	Microcryst.	58·3	4·4	$C_{20}H_{18}O_6N_2$	58·0	4·4
Me	Bu^n	154	$CHCl_3$–MeOH	Prismatic needles	60·4	5·1	$C_{23}H_{24}O_6N_2$	60·5	5·3
H	Bu^n	220 †	Et_2O–Pet	Plates	59·2	4·7	$C_{21}H_{20}O_6N_2$	58·9	4·7
Me	*iso*-C_5H_{11}	180—181	$CHCl_3$–EtOH	Needles	61·2	5·3	$C_{24}H_{26}O_6N_2$	61·3	5·6
H	*iso*-C_5H_{11}	255 †	Et_2O–Pet	Needles	59·7	4·8	$C_{22}H_{22}O_6N_2$	59·7	5·0
Me	*n*-C_6H_{13}	123—124	MeOH	Prismatic needles	61·75	5·7	$C_{25}H_{28}O_6N_2$	62·0	5·8
H	*n*-C_6H_{13}	225—227 †	Et_2O–Pet	Prismatic needles	60·7	5·0	$C_{23}H_{24}O_6N_2$	60·5	5·3

* Pet = light petroleum (b. p. 60—80°). † With decomp.

1 : 2-*Di*-(3-*acetoxy*-4-*methoxycarbonylphenyl*)-4-n-*butyl*-3 : 5-*dioxopyrazolidine* (VI; R = Me, R′ = OAc, R″ = Bu^n).—Condensation of *n*-butylmalonyl chloride was carried out as described above, with the difference that the ethereal solution of the product was extracted with 5%

aqueous sodium carbonate instead of 2% potassium hydroxide. The extract was acidified (Congo-red) with hydrochloric acid and the product isolated by means of ether. Crystallisation from ether–light petroleum (b. p. 100—120°) and then from light petroleum (b. p. 100—120°) gave **1** : 2-*di*-(3-*acetoxy*-4-*methoxycarbonylphenyl*)-4-n-*butyl*-3 : 5-*dioxopyrazolidine* as felted needles, m. p. 143—144° (Found : C, 60·3; H, 5·1. $C_{27}H_{28}O_{10}N_2$ requires C, 60·0; H, 5·2%). This compound (m. p. and mixed m. p. 142—143°) was also obtained by treatment of 4-*n*-butyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidine with pyridine and acetic anhydride at room temperature overnight.

4-*Alkyl*-1 : 2-*di*-(4-*carboxy*-3-*hydroxyphenyl*)-3 : 5-*dioxopyrazolidines*.—A solution of the 1 : 2-di-(4-alkoxycarbonyl-3-hydroxyphenyl)-4-alkyl-3 : 5-dioxopyrazolidine (0·5 g.) in 5% potassium hydroxide (20 c.c.) was heated on the steam-bath for 30 min. The cooled solution was acidified (Congo-red) with hydrochloric acid, the solid collected, and crystallised. The acids (Table 2; yields, 50—70%) give a purple colour with aqueous ethanolic ferric chloride and dissolve with effervescence in aqueous sodium hydrogen carbonate.

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Absorption Spectra and Structure of Sulphinic Acids.

By (MISS) S. DETONI and D. HADŽI.

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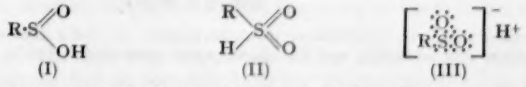
Of the two possible structures (I) and (II) for sulphinic acids the former is favoured on ground of infrared and ultraviolet spectra. Probable assignments have been made of infrared bands in the spectra of benzene-, toluene-*p*-, naphthalene-2-, and *o*-methoxybenzene-sulphinic acids, and their esters, salts, and chlorides. The dissociation equilibria of benzenesulphinic acid in dry and moist carbon tetrachloride have been studied, and the character of the association discussed.

LITTLE work has been done on the structure of the sulphinic acid group since the publication by Otto and Rössing (*Ber.*, 1892, **25**, 230), in which they showed that ions of aromatic sulphinic acids may react in two different forms. With alkyl halides, the salts yield sulphones, but with ethyl chlorocarbonate they give esters. Connor in Gilman's " Organic Chemistry " (Vol. I., 1948, p. 914) discusses the two possible tautomeric forms (I) and (II) and concludes that sulphinic acids are best formulated as (III). This implies, however, some sort of fast proton oscillation between unequivalent positions, which is rather unlikely.

Guryanova and Syrkin (*Zhur. fiz. Khim.*, 1949, **23**, 105) determined the dipole moments of some aromatic sulphinic acids in benzene and dioxan solutions and compared their experimental values with those calculated for structures (I) and (II), assuming a planar arrangement of the atoms in (I). The measured moments lay between the two calculated



(I) (II) (III)

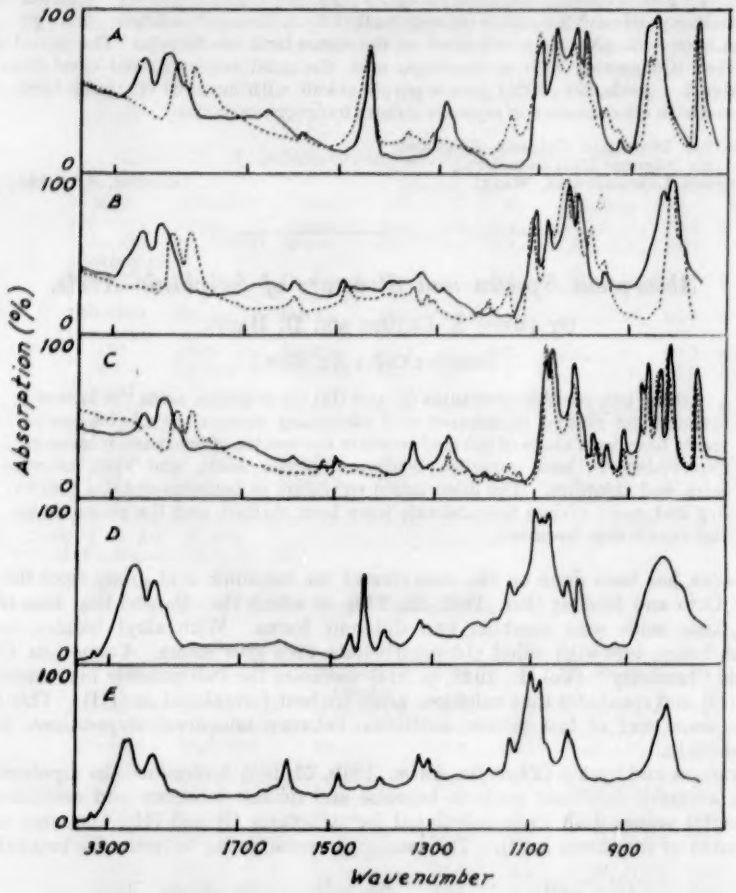
values, and the authors concluded that sulphinic acids in solution were a mixture of both tautomeric forms. The same authors published also infrared spectra of some solid sulphinic acids in the high-frequency region as well as Raman data for solutions in dioxan. Two peaks are apparent, at 2500 and 2560 κ * respectively, the latter being assigned to a S–H frequency, in agreement with the conclusion derived from dipole-moment determinations.

* The use of the symbol κ (Kayser) for cm.$^{-1}$ is optional in Chemical Society publications (*cf.* Lecomte, *J. Opt. Soc. Amer.*, 1953, **43**, 410; see *Ann. Reports*, 1954, **51**, 12).

The only other spectroscopic work on sulphinic acids is that by Houlton and Tartar (*J. Amer. Chem. Soc.*, 1938, **60**, 544) on Raman spectra of sulphinic salts in water.

More attention has been paid to the structure of sulphinic esters. Phillips (*J.*, 1925, 2553) resolved several *n*-alkyl toluene-*p*-sulphinates and concluded that the sulphinic ester group was pyramidal with the sulphur atom at the apex. Ziegler and Wenz (*Annalen*,

FIG. 1. *Infrared spectra of sulphinic acids* (———) *and deuterated sulphinic acids* (– – – – –).



A, Solid benzenesulphinic acid. B, Solid toluene-p-sulphinic acid. C, Solid naphthalene-2-sulphinic acid. D, Benzenesulphinic acid in $CHCl_3$, *and E, toluene-p-sulphinic acid in* $CHCl_3$ (*both* 0·2 *mole/l.*; 0·1-*mm. cell*).

1934, **511**, 109) reached the same conclusion for some other sulphinic esters. Parachor determinations by Sugden, Reed, and Wilkins (*J.*, 1925, 1525) indicate that one S:O group in the sulphinic esters has sulphoxide character. The near-ultraviolet absorption spectrum of methyl toluene-*p*-sulphinate (Bredereck, Bäder, and Höschele, *Chem. Ber.*, 1954, **87**, 784) showed an auxochromic effect of the sulphinic ester group (log ε 3·5) which was used as evidence for strong conjugation between the aromatic ring and this group.

The present authors were interested primarily in the hydrogen bonding in sulphinic

acids, but more reliable proofs of the structure were required first; the infrared and ultraviolet spectra have been determined for a series of sulphinic acids and their salts, esters, and chlorides.

Infrared Spectra.—In the spectra of the solid sulphinic acids investigated, three groups of strong bands seem to appear consistently in the regions 2790—2340, 1090—990, and 870—810 K respectively (Fig. 1, *A*—*C*). Guryanova and Syrkin (*loc. cit.*) do not list exact positions of both high-frequency bands, but in general appearance their curves are similar to ours. There are considerable differences between the spectra of solid acids and their solutions in carbon tetrachloride or chloroform (Fig. 1, *D*, *E*). Both the high-frequency sets of bands move to higher frequency in solution, their position being now near 2900 and 2500 K, and their relative intensities also change. In sufficiently dilute solution a new band appears also at 3700 K in carbon tetrachloride, or at 3600 K in chloroform. The apparent molal extinction coefficients of this group of bands for benzenesulphinic acid are listed in Table 1 and discussed below. Instead of several bands near 1050 K in the solid, a doublet appears in solution some 30 K lower, and the band near 850 K also shifts to somewhat higher frequencies in solution.

The solution work is rendered difficult by the instability of sulphinic acids, particularly

TABLE 1. *Effect of solvent upon the* OH *absorption in benzenesulphinic acid.*

Concn.	3700 K		2900 K			2500 K		
(mole/l.)	T (%)	ε	T (%)	ε	$C\varepsilon_m^2/\varepsilon$	T (%)	ε	$C\varepsilon_m^2/\varepsilon$
			Dry CCl_4 (*cell length* 50 *mm.*)					
0·002	71	15	13	89	0·005	20	70	0·006
0·0015	68	22	21	90	0·008	28	74	0·010
0·001	70	31	35	91	0·012	42	75	0·014
0·0008	67	44	42	94	0·016	49	77	0·019
0·0006	70	52	52	95	0·017	58	79	0·020
0·0004	73	68	64	99	0·019	69	82	0·023
			Moist CCl_4 (0·04% *of* H_2O) (*cell length* 20 *mm.*)					
0·003	80	16	29	84	0·009	39	68	0·011
0·0025	79	20	37	86	0·010	45	69	0·012
0·002	82	22	45	87	0·011	52	71	0·013
0·0015	77	38	51	97	0·022	59	76	0·028
0·001	76	60	63	100	0·036	70	77	0·046
0·0008	75	78	68	105	0·046	74	78	0·062

at slightly elevated temperatures. Amongst the products of decomposition are the related sulphonic acids (Pauly and Otto, *Ber.*, 1877, **10**, 2181), the presence of which is shown by the bands near 1200 and 1340 K (Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397), which become strong in *ca.* 10 hr. at room temperature.

The deuterated analogues show a most remarkable change in the high-frequency region. Instead of the bands near 2760 and 2350 K new ones appear near 2080 and 1850 K respectively in the solid. In the spectra of deuterated benzene- and naphthalene-sulphinic acids respectively three peaks are visible in this region. Some peaks near 1050 K are shifted slightly towards higher frequencies, whereas a medium band seem to shift from 1280 to 950 K. The bands near 840 K are also slightly affected by deuteration. The differences between the spectra of solids and of solutions are similar to these found with undeuterated acids.

In the spectra of the sulphinic esters the strong band in the middle region of the spectrum appears again, but at somewhat higher frequencies than in the acids (1126—1136 K). Other characteristic bands seem to be one near 960 K, and perhaps a broad band near 750 K.

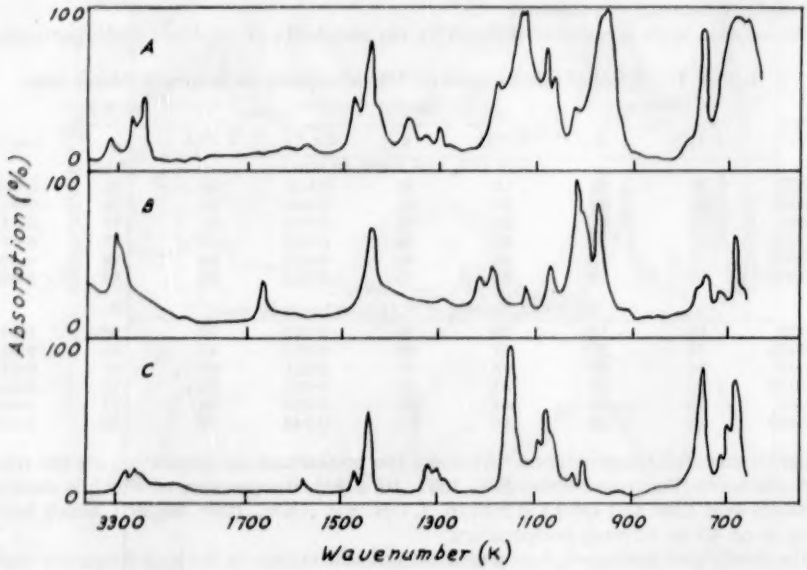
The spectra of acid chlorides contain only one strong band, near 1150 K, whereas the salts show strong absorption mear 1020 and 980 K, positions which correspond well to those of the Raman bands (Houlton and Tartar, *loc. cit.*). The spectra of derivatives of the benzenesulphinic acid only are reproduced in Fig. 2, the spectra of derivatives of other acids being similar.

If structure (II) represents the sulphinic acid group, we should expect to find two

strong bands near 1350 and 1150 K arising from the symmetric and the antisymmetric stretching vibrations respectively of the O:S:O group (cf. the sulphones; Barnard, Fabian, and Koch, *J.*, 1949, 2442; Price and Gills, *J. Amer. Chem. Soc.*, 1953, **75**, 4750) and sulphonic acids (Haszeldine and Kidd, *J.*, 1954, 4228). In the latter compounds, the higher-frequency band seems to be the stronger. However, in the spectra of sulphinic acids, the main absorption band in solution is near 1090 K, reminiscent of the characteristic band of the sulphoxides near 1050 K (Barnard *et al.*, *loc cit.*). No strong bands appear between 1300 and 1400 K.

The assignment of the 1090 K band to the S:O group in the acids is confirmed by the presence of a similar band in the spectra of the acid chlorides and particularly of the esters, the structure of the latter having been ascertained by the work of Phillips and of Ziegler (*loc. cit.*). The frequency of the S:O band in the esters is higher than in the corresponding

FIG. 2. *A, Methyl benzenesulphinate, liquid film. B, Potassium benzenesulphinate, solid. C, Benzene sulphinyl chloride, liquid film.*



acids. This recalls a similar relation in the carboxylic series. Barnard *et al.* (*loc. cit.*) also mentioned the influence of negative substituents on the S:O bond, which consisted in a rise of its stretching frequency. The lower frequency of the S:O group in the acids may be due in part also to hydrogen bonding.

Probable assignments may be made for the remaining characteristic bands, the high-frequency ones being discussed in connection with the hydrogen bonding. The band near 860 K in the spectra of sulphinic acids may be due to the stretching of the S–O bond. The force constants of the sulphur–oxygen bonds are weakened by approximately 40% relatively to analogous carbon–oxygen bonds (Kohlrausch, "Ramanspektren," Akad. Verlagsgeselschaft, Leipzig, 1943, p. 416). Thus, taking the stretching frequency of the C–O bond in carboxylic acid dimers to be near 1300 K (Hadži and Sheppard, *Proc. Roy. Soc.*, 1953, **216**, 247), we should expect to find the band corresponding to the S–O linkage near 800 K. This is in a satisfactory agreement with the above assignment. Bands with similar frequencies appear also in the infrared spectra of sulphonic acids, as well as in their Raman spectra; Maschka and Aust (*Monatsh.*, 1954, **85**, 891) assigned these also to the S–O stretching mode. In the spectra of the sulphinic salts the bands due to the S:O

group seem to be shifted to lower frequencies, whereas the corresponding S–O band appears at higher frequencies (960 K). This is similar to the behaviour of the C:O and C–O bands in carboxylic acids on ionisation, and may be explained accordingly by the resonance

The shift of the band near 1280 K in the spectra of sulphinic acids to lower frequency on deuteration, the ratio of the frequencies being near 1·4, suggests that this band is due to a motion of the OH group, probably a deformation mode. This frequency compares well with the in-plane deformation frequency of the OH group in carboxylic acid dimers (Hadži and Sheppard, *loc cit.*) and peroxy-acids (Giguère and Olmos, *Canad. J. Chem.*, 1952, **30**, 821). The intensity of this band, if compared to that due to S:O stretching, seems to be much smaller than that of the analogous band in the carboxylic acids. Dr. N. Sheppard suggested that in carboxylic acids the δ(OH) may be abnormally strong because of interaction with the nearby CO frequency.

Hydrogen bonding in sulphinic acids. In agreement with the above assignments, which leave little doubt as to the correctness of structure (I), the band near 2900 and 2500 K must belong to the stretching vibrations of bonded OH groups, and the sharp band at 3700 K which appears in dilute solution is doubtless due to the OH stretching of the monomeric acid. The band near 2900 K appears at a frequency not unusually low for strongly bonded OH groups, and the shift to 2180 K on deuteration is in agreement with this assignment. A number of cases is known in which strongly shifted OH bands are observed, having positions near to 2500 K (Lord and Merrifield, *J. Chem. Phys.*, 1953, **21**, 166; Angel and Werner, *Austral. J. Chem.*, 1953, **6**, 294) similar to that of the second band in sulphinic acids. This band might be mistaken for a S–H band because of its low frequency, as assumed by Guryanova and Syrkin (*loc. cit.*). However, their finding that the Raman line at 2550—2560 K is weak, is in agreement with our assignment, since SH groups give rise to strong Raman lines, whereas OH groups are weak in scattering and strong in infrared absorption.

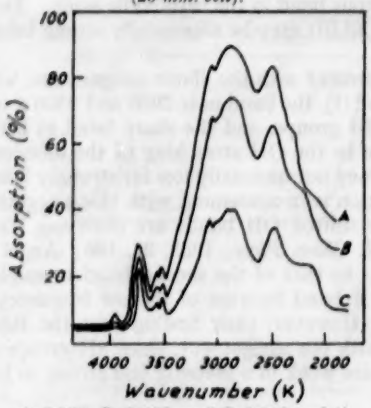
More information about the association of the sulphinic acids through hydrogen bonds may be gathered from the trends of the extinction coefficients of the OH bands at various concentrations. Measurements with benzenesulphinic acid in carbon tetrachloride are collected in Table 1. Wright (*J.*, 1949, 683) has shown that the degree of association of sulphinic acids depends considerably on small quantities of water present in the solvent. Therefore one series of measurements was carried out in carefully dried carbon tetrachloride and, in a second, water was added. Cells with an optical path of 50 mm. were used in the first series of the measurements, since the absorption of the monomer was very small at shorter path lengths. The absorption of water in the moist solvent (water content 0·04%) interfered too strongly with the monomer band in 50-mm. cells, therefore the second series had to be done with a 20-mm. path length, the absorption of the monomer in moist solvent being sufficiently strong. The peak absorptions were used in subsequent calculations, although it would be more correct to use integrated absorptions. However, the latter method was not applicable, because the low-frequency side of the band, culminating near 2500 K, merges with the absorption of the solvent and therefore the energy transmitted here was too low for quantitative work. The ratio $C\varepsilon_m^2/\varepsilon$ (where C is the concentration of the acid in mole/l., ε the extinction coefficient of the associated band, and ε_m the extinction coefficient of the monomer), varies by as much as 35% in dry solvent, and 50% in moist solvent over the range investigated. This indicates that benzenesulphinic acid forms polymers of an order higher than two. A similar result has been obtained recently by Klemperer, Cronyn, Maki, and Pimentel (*J. Amer. Chem. Soc.*, 1954, **76**, 5846) for secondary amides.

Attempts have been made to determine the fraction α of unassociated molecules by extrapolating the plots of log I_0/C log I *versus* C to zero concentration, and calculating therefrom the dissociation constant K_c (Kempter and Mecke, *Z. phys. Chem.*, 1941, **46**, *B*, 229). However, for small concentrations the data obtainable with the cell length

which could be used were insufficiently accurate. Apparently, there is less dissociation to monomers in solvent containing water, in agreement with Wright's result. The dissociation constants, $K_c = \alpha C/(1-\sqrt{\alpha})$, were of the order of 10^{-4} in dry solvent, and 10^{-3} in moist solvent.

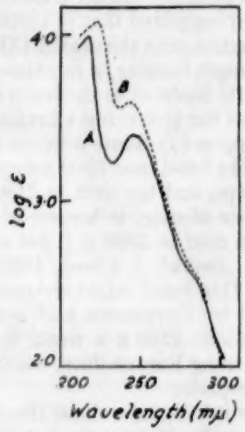
The hydrogen bond in the solid seems to be stronger, since both bands due to bonded hydroxyl are shifted to lower frequencies; also the sulphoxide band is considerably lowered in frequency. The splitting of the latter band, which is particularly well pronounced in the spectra of the solids, may be due to the coupling of similar groups in a chain. This is also the probable cause of the appearance of several bands due to OH groups. Although in the solid and in concentrated solution two bands only are recorded, that near 2900 K

FIG. 3. *Benzenesulphinic acid in* CCl_4 *(20-mm. cell).*



A, 0·005, *B*, 0·003, *and C*, 0·001 *mole/l.*

FIG. 4. *Ultraviolet spectra of (A) benzenesulphinic and (B) toluene-p-sulphinic acid.*



shows distinctly a composite character at lower concentrations (Fig. 3), and in the spectrum of deuterated benzenesulphinic acids three bands were clearly resolved. This region of the spectrum of sulphinic acids may be compared with that for solid formic acid, the latter showing peaks at 3226, 2890, 2703, and 2538 K (Bratož, Hadži, and Sheppard, unpublished work). Solid formic acid forms polymer chains by association (Holtzberg, Post, and Fankuchen, *Acta Cryst.*, 1953, **6**, 127). With reference to the strong shift of the OH band, the authors hope to obtain more information about the strength of the hydrogen bonds in sulphinic acids.

Ultraviolet Spectra.—The sulphinic group causes a bathochromic shift of the ultraviolet absorption of the benzene nucleus, its group *p* band moving to 218 (benzenesulphinic acid) or 223 mμ (toluenesulphinic acid), with an increase in intensity (Fig. 4). The vibrational

TABLE 2.

	$\lambda_{max.}$ (mμ)	log ε
Benzenesulphinic acid	218	3·99
	245	3·40
Toluene-*p*-sulphinic acid	223	4·09
	242	3·59
Methyl benzenesulphinate	223·5	3·94
	241·5	3·59
Methyl phenyl sulphoxide *	250	3·6
Methyl phenyl sulphone *	266	2·9
	273	2·8
Methyl *p*-ethoxycarbonylbenzenesulphinate *	272	4·0
,, *p*-ethoxycarbonylbenzenesulphonate *	279	3·2
,, *m*-ethoxycarbonylbenzenesulphinate *	250	3·6
,, *m*-ethoxycarbonylbenzenesulphonate *	374	2·85

* Price and Hydock, *J. Amer. Chem. Soc.*, 1952, **74**, 1943.

structure of the group α band is slightly indicated in the esters only. The position of this band is little changed with respect to benzene; the intensity is, however, increased. It appears from the published data on the absorption of aromatic sulphones and sulphoxides that the S:O group intensifies the absorption of the aromatic nucleus more than does the sulphone group (Table 2). The extinction coefficient of the group α band in benzenesulphinic ester compares well with that of methyl phenyl sulphoxide and it is well above that of methyl phenyl sulphone. This fact, taken together with the similarity in the absorption of the respective acids, is an additional proof of the correctness of structure (I).

Experimental

Preparation of Substances.—Benzene-, toluene-*p*-, and naphthalene-2-sulphinic acid were prepared by reduction of the sulphonyl chlorides (Smiles and Bere, *Org. Synth.*, Coll. Vol. I, 1932, p. 7). *o*-Methoxybenzenesulphinic acid was prepared by Gattermann's method (*Ber.*, 1899, **32**, 1142). The acids were recrystallised several times from water and kept over silica gel for drying. Carefully purified samples could be kept in an ice-chest unchanged for several months. Esters were prepared by Phillips's method (*J.*, 1925, **2553**), and distilled in a high vacuum. Sulphinyl chlorides were prepared by Hilditch and Smiles's method (*Ber.*, 1908, **41**, 4113). Deuterated sulphinic acids were prepared by hydrolysis of the corresponding chlorides with deuterium oxide.

The spectra were recorded with a Perkin–Elmer infrared spectrometer Model 21, equipped with sodium chloride and lithium fluoride prisms. The solids were examined as mulls in Nujol and hexachlorobutadiene. Carbon tetrachloride was dried by refluxing over phosphoric oxide, and chloroform over potassium carbonate. Solutions were made by weighing for each dilution, and were shaken mechanically for 2 hr. No decomposition of sulphinic acids was observed during this time. Solutions in moist carbon tetrachloride were prepared by adding the necessary amount of water to dry solvent. All operations were executed in a constant-temperature room (22° ± 1°). Quantitative absorption determinations were carried out in two separate series of dilutions.

Ultraviolet spectra were measured with a Beckman DU Spectrophotometer, the readings being taken each 0·5 or 1 mμ. Ethyl alcohol was used as solvent.

The authors express their indebtedness to Dr. N. Sheppard for a critical reading of the paper.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLII. Introductory Remarks, and Kinetics of the Interaction of Chloride Ions with Simple Alkyl Chlorides in Acetone.*

By P. B. D. de la Mare.

[Reprint Order No. 6206.]

The background and scope of a group of closely related papers are indicated. Kinetic experiments on the second-order reactions of chlorine exchange between lithium radio-chloride and three simple alkyl chlorides in acetone are reported. Rate constants and parameters of the Arrhenius equation are evaluated.

Introduction to a Group of Papers.—Our knowledge of the bimolecular mechanism of nucleophilic substitution (S_N2) is now so far developed that further significant advance is likely to come mainly from quantitative approaches; and for study on such lines the

* Part XLI, *J.*, 1954, 2939.

simplest systems are the most profitable. Finkelstein's reaction of halide replacement in alkyl halides by attacking halide ion offers a maximum of simplicity, inasmuch as both the substituting agent and the displaced group are monoatomic. Moreover, they can be made identical, and the reaction can still be studied with the aid of isotopic labelling, so that, for a given alkyl group, we can have, not only the substitution involving the fewest possible atoms, but also that involving the fewest kinds of atom, and therefore a theoretical problem already partly simplified by its symmetry.

For these reasons it was decided to build up a body of data on rates and their temperature coefficients for Finkelstein reactions of simple, substituted, and cyclic alkyl halides. The work is still incomplete, but has been followed far enough to justify, it is thought, the report which the present group of papers constitutes.

The bimolecular mechanism of substitution being now the main subject of interest, acetone was the first solvent used in this work, though it has been extended to other solvents since. The merit of acetone is that it dissolves many ionic halides, and yet is not so highly ionising that it fails to retain the Finkelstein substitutions in their bimolecular form. In fact, it preserves the bimolecular mechanism over a wide variety of alkyl structures, thereby permitting most of the kinetic comparisons which it was desired to make. And it cannot solvolytically substitute the alkyl halides. The present papers are restricted to an account of reactions conducted in homogeneous solution in dry acetone.

With four halogens, sixteen types of Finkelstein reaction are possible; but, for homogeneous reactions in acetone, the seven which depend on fluorine have to be excluded as involving inconveniently low solubilities. Of the nine substitutions dependent only on chlorine, bromine, or iodine, seven have so far been examined for simple alkyl groups in solvent acetone. Certain classes of modified alkyl groups, such as aralkyl and alicyclic groups, have been studied also, usually with respect to one type of substitution only.

As to the history of kinetic study of the Finkelstein reaction, the basic exploratory work of Conant, Kirner, and Hussey (*J. Amer. Chem. Soc.*, 1924, **46**, 232; 1925, **47**, 476, 488) showed that, in acetone, the reactions of potassium, sodium, and lithium iodides with alkyl chlorides were kinetically of the second order, *i.e.*, first order in each reactant. Rate comparisons were made for a considerable number of alkyl groups, though many of the actual rates were somewhat inexact, partly because, when potassium and sodium salts were used, the solutions did not remain homogeneous. Of subsequent investigations, the more extensive have employed solvents, such as ethyl alcohol or aqueous acetone (Seelig and Hull, *ibid.*, 1942, **64**, 940; McKay, *ibid.*, 1943, **65**, 702; le Roux, Lu, Sugden, and Thomson, *J.*, 1945, 586), which are not as suitable as is dry acetone for the purpose of maintaining the bimolecular mechanism and avoiding solvolytic side-reactions over a range of alkyl groups, including tertiary groups. In all the above work, moreover, salt effects, which are not negligible, were not standardised. A number of investigations have employed dry acetone as solvent, but have dealt with a single case, or a very few cases, often in order to illustrate some special phenomena, such as the Walden inversion, or anionotropy, or salt effects (Hughes, Juliusberger, Masterman, Topley, and Weiss, *J.*, 1935, 1525; Bartlett and Rosen, *J. Amer. Chem. Soc.*, 1942, **64**, 543; Dostrovsky and Hughes, *J.*, 1946, **161**; Evans and Sugden, *J.*, 1949, 270; England and Hughes, *Nature*, 1951, **168**, 1002; McKinley-McKie and Moelwyn-Hughes, *J.*, 1952, 838). Similar restrictions of scope apply to most investigations of Finkelstein substitutions with modified alkyl groups (Juvala, *Ber.*, 1930, **63**, 1539; Hughes, Juliusberger, Scott, Topley, and Weiss, *J.*, 1936, 1173; Cowdrey, Hughes, Nevell, and Wilson, *J.*, 1938, 209; Bither, Sturtevant, and Thomas, *J. Amer. Chem. Soc.*, 1945, **67**, 1562; Solomon and Thomas, *ibid.*, 1950, **72**, 2024; Bordwell and Cooper, *ibid.*, 1951, **73**, 5034; Olson, Frashier, and Spieth, *J. Phys. Colloid Chem.*, 1951, **55**, 860; Hatch *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 6002, and earlier papers of the series; Vernon, *J.*, 1954, 4462), but exception must be made of some systematic studies with *cyclo*alkyl halides (van Stratten, Nickolls, and Winkler, *Canad. J. Chem.*, 1951, **29**, 373; Roberts and Chambers, *J. Amer. Chem. Soc.*, 1951, **73**, 5034; Fierens and Verschelden, *Bull. Soc. chim. Belg.*, 1952, **61**, 427). Further rate data on substitutions of simple alkyl halides are given by le Roux and Swart (*J.*, 1955, 1475).

The new rate measurements for Finkelstein substitutions with simple alkyl groups

are given in Parts XLII—XLVIII, and are collectively discussed in Part XLIX. Some preliminary and partial reports of them have appeared already (de la Mare, England, Fowden, Hughes, and Ingold, *J. Chim. phys.*, 1948, **45**, **236**; Hughes, *J.*, **1949**, S **400**; de la Mare, *Ind. chim. Belg.*, **1950**, **15**, 189; Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, **1953**, p. 408). Some results for certain modified alkyl groups will be presented later.

Reactions of Chloride Ions with Alkyl Chlorides.—As far as the author is aware, chlorine exchange by the Finkelstein reaction in simple aliphatic halides has not been studied before, though the exchange has been observed in *p*-nitrobenzyl chloride (Bither, Sturtevant, and Thomas, *loc. cit.*).

In the present experiments, the exchange, followed in anhydrous acetone, was between methyl, ethyl, and *iso*propyl chlorides and chloride ion, which was supplied as lithium chloride containing the radioactive isotope ^{36}Cl. The results are in Table 1. The counting

TABLE 1. *Second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of chlorine exchange between lithium radio-chloride and alkyl chlorides in acetone.*

Temp. (c)	a = [AlkCl]	b = [LiCl]	Counting rates C	$C-X_1$	$C-X_2$	t_2-t_1 (min.)	10^5k_2	10^5k_2 (Mean)
			Methyl chloride.					
+44·6°	0·2805	0·0267	154·5	152·1	129·4	35·6	28·5	
					117·1	46·3	35·1	
					109·3	56·6	36·2	
					113·7	66·2	27·3	31·8
+25·0	0·2905	0·0275	154·5	—	66·1	1353	3·78	
					65·0	1366	3·83	
					61·9	1374	4·04	3·88
− 3·2	0·3038	0·0286	154·5	—	99·2	20170	0·121	
					95·0	24450	0·110	
					86·8	30205	0·107	
					89·3	30450	0·100	0·109
			Ethyl chloride.					
+60·5	0·2285	0·0258	131·2	128·4	73·3	1788	2·39	
					75·1	1852	2·20	
					50·9	2824	2·60	2·40
+39·6	0·2356	0·0266	132·4	—	81·3	11470	0·311	
					83·5	11638	0·289	
					67·9	15217	0·326	0·309
+25·1	0·2411	0·0272	111·0	—	85·9	36010	0·050	
					80·2	41850	0·055	
					74·0	47990	0·061	0·055
			*iso*Propyl chloride.					
+60·1	0·2219	0·0283	162·0	—	78·5	131040	0·0442	
					81·3	131040	0·0419	
					75·1	131040	0·0471	
+60·1	0·2219	0·0283	162·6	—	59·8	169920	0·0488	0·0455

rates, C, $C-X_1$, and $C-X_2$, measure, respectively, specific activities in the inorganic chloride initially, on separation at a time t_1 soon after the reaction solution had attained thermostat temperature, and on separation at a later time t_2. The spread of the calculated second-order rate constants k_2 for each temperature is typical of such experiments, and arises mainly from random fluctuations in the counts recorded within finite time intervals. Usually, counts of about 10,000 were taken on each sample, and it can be computed that this number should lead to probable errors in individual rate constants of about 3%. Consistently, the standard deviation of the rate constants from their means averages about 5%.*

The exchanges of methyl chloride and ethyl chloride were studied each at three temperatures. However, the exchange of *iso*propyl chloride was examined only at 60°. At

* This is consistent, because, when both concepts are significant in relation to the same data, the probable error is 0·67 times the standard deviation. Here each reading has a probable error, but not a standard deviation, whereas the collection has a standard deviation, but not, except formally, a probable error.

this temperature a period of 3 months was required in order to obtain a convenient amount of exchange, and hence no experiments at lower temperatures were tried. Attempted experiments at the higher temperatures, 79° and 100°, failed, for the reason that lithium chloride, which has a negative temperature coefficient of solubility in acetone, crystallised from the solutions. Because of these difficulties with *iso*propyl chloride, no attempt was made to extend the work to *tert.*-butyl chloride, which in bimolecular substitutions is still less reactive.

As will be illustrated in several of the following papers, Finkelstein substitutions in acetone are subject to a negative salt effect, which requires the standardisation of salt concentrations in any comparison of rates. In the present work, the kinetic salt effect was not directly measured, but, in the experiments here quoted, it was standardised by maintaining the concentrations of lithium chloride close to 0·027M.

The main results of this investigation are summarised in Table 2. They show that, in

TABLE 2. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), relative rates at common temperatures, and Arrhenius parameters (B_2 in sec.$^{-1}$ mole^{-1} l., and E_A in kcal. mole^{-1}) of reactions of lithium radio-chloride with alkyl chlorides in acetone.*

	10^5k_2 (25°)	10^5k_2 (60°)	Rel. k_2 (25°)	Rel. k_2 (60°)	$\log_{10} B_2$	E_A
MeCl	3·88	140	71	57	10·3	20·1
EtCl	0·055	2·45	1	1	9·5	21·5
Pr^{i}Cl	—	0·045	—	0·019	—	—

the series MeCl, EtCl, Pr^{i}Cl, the rates of chlorine exchange by the Finkelstein reaction decrease with branching homology in steps of 50- to 80-fold, and that, for MeCl and EtCl, the parameters of the Arrhenius equation $k_2 = B_2 \exp(-E_A/RT)$ indicate that the fall in rate from methyl to ethyl is due in part to a decrease in the probability, and in part to an increase in the energy of the transition state of the reaction of the higher alkyl group.

EXPERIMENTAL

Lithium radio-chloride was prepared by a Szilard–Chalmers separation from potassium perchlorate, which had been irradiated for one month in the Harwell pile under a flux of 10^{10} neutrons per cm.^{2} per sec., and kept for a further month in order to allow decay of most of the potassium activity. To a solution of this material in water, a small amount of sodium chloride was added as carrier, and then the chloride was precipitated as silver chloride, and converted by reduction with hydrogen at red heat into hydrogen chloride, and thence into lithium chloride, which was purified with the aid of acetone, and dried.

"AnalaR" acetone was dried with calcium chloride, and distilled with a little quinol through an efficient column at high reflux ratio. Sufficient for each kinetic run was distilled from anhydrous magnesium perchlorate immediately before use.

The dried and redistilled alkyl chloride was introduced by distillation into a solution of lithium radio-chloride, in a closed system designed to permit the subsequent operations without loss of the volatile materials. The original lithium chloride solution having been standardised with respect to chloride ion, the concentration of alkyl chloride was determined by estimation of total chloride after reaction with silver nitrate at 100°. Samples for radiochemical analysis were evaporated at a low temperature, and the residual salt was dissolved in water. The radioactivity was measured with the type of counter usual for liquid samples, and the standard counting equipment.

If a and b are respectively the concentrations of alkyl chloride and lithium chloride, and if C and $C - X$ are respectively the specific radioactivities of the initial solution of lithium chloride and of a solution of the salt recovered from a reaction stopped after a time t, the second-order rate constant is given (le Roux and Sugden, *J.*, 1939, 1279) by the equation,

$$k_2 = \frac{2{\cdot}303}{(a+b)t} \log_{10}\left[1 - \frac{X}{C}\left(1 + \frac{b}{a}\right)\right]^{-1}$$

Although it made little difference to the calculation of the present results, this equation was sometimes used in a form which allowed for the reaction's occurring during the time the reaction mixture took to reach thermostat temperature. This involved measurement of the specific

activity X_1 at a time t_1 soon after the solution had attained the proper temperature, and the specific activity X_2 at a later time t_2. The appropriate form of equation is as follows:

$$k_2 = \frac{2{\cdot}303}{(a+b)t} \log_{10} \left\{ [1 - \frac{X_1}{C}(1 + \frac{b}{a})][1 - \frac{X_2}{C}(1 + \frac{b}{a})]^{-1} \right\}$$

In use of these formulæ, the concentrations a and b are computed with due allowance for the change of volume of the solvent between the temperature of standardisation and the temperature of reaction.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLIII. Kinetics of the Interaction of Chloride Ions with Simple Alkyl Bromides in Acetone.*

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[Reprint Order No. 6207.]

Kinetic experiments on the second-order reactions of halogen substitution by lithium chloride with seven simple alkyl bromides in acetone are reported. The reactions are only mildly reversible. The second-order substitution with *tert.*-butyl bromide is accompanied by a minor amount of an elimination of lower reaction order, probably first. Rate constants and the parameters of the Arrhenius equation were determined for all the substitutions.

OLSON and his co-workers studied the concurrent reactions which occur in solvent water between chloride ion and bromosuccinic acid, and between chloride ion and α-bromophenylacetic acid (Olson and Long, *J. Amer. Chem. Soc.*, 1934, **56**, 1294; 1936, **58**, 393; Young and Olson, *ibid.*, p. 1157). Solomon and Thomas examined the reactions in aqueous acetone of lithium chloride with two alkyl bromides and with three bromides of the *cyclo*hexane series (*ibid.*, 1950, **72**, 2028). We cannot recall a previous investigation of the kinetics of displacement of bromine from alkyl bromides by substituting chloride ion in dry acetone as solvent.

In this paper an investigation is described of the kinetics of the reaction in dry acetone between lithium chloride and seven alkyl bromides. The alkyl groups were the simplest of those calculated to bring out the more general polar and steric effects of alkyl structure on bimolecular nucleophilic substitution: they comprise the two branching-homologous series, which we call the α- and β-methylated alkyl series (*neo*Pe = *neo*pentyl):

Me, Et, Pr^i, Bu^t	Et, Pr^n, Bu^i, *neo*Pe
α-Methylated series	β-Methylated series

The progress of the forward reaction, $Cl^- + RBr \rightleftharpoons RCl + Br^-$, was followed by electrometric titration of the inorganic salts with silver nitrate, after removal of the organic material. Under conditions which minimise coprecipitation of the silver halides, two equivalence points are found, one for bromide ion, which measures the progress of reaction, and the second for total halide ion. The constancy in the latter establishes that the reaction consists wholly of substitution. Six of the seven reactions examined were in fact pure substitutions, while the remaining one was shown to be predominantly a substitution.

The reactions run to equilibrium. However, in our conditions, the equilibria lay so far towards the right-hand side of the above equation, that 70% or more of the forward process could be followed without sensible disturbance from reversibility. We could

* Part XLII, preceding paper.

therefore simplify the work by omitting the determination of equilibrium constants, and computing second-order rate constants from the kinetic equation for an irreversible reaction.*

With reservations applying to one case, the reactions were kinetically of second order, and showed negative salt effects. We did not make any detailed study of salt effects, but secured comparable rate constants for the evaluation of their temperature coefficient by using standardised salt concentrations. These were 0·05M for the reaction of methyl bromide, and 0·07M for the reactions of its homologues. It has been shown for related Finkelstein reactions that kinetic salt effects do not perceptibly influence the Arrhenius activation energies.

The case which called for special treatment was that of *tert.*-butyl bromide. Its reaction with chloride ion, as measured by the development of bromide ion, was found to be only roughly of second order. Moreover, the criterion for a pure substitution by constancy of total inorganic halide was not fulfilled: the amount of total halide ion rose as reaction progressed, indicating that some elimination was taking place; and this interpretation was confirmed by following the concurrent development of acid. Now it has been shown (de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930) that, in solvent nitromethane, the reaction between chloride ion and *tert.*-butyl bromide is entirely unimolecular, and consists wholly, or almost wholly, of elimination. Therefore we conclude that, even in dry acetone, *tert.*-butyl bromide undergoes some ionisation, with the result that a predominating bimolecular substitution is accompanied by a side reaction consisting mainly at least of elimination:

$$Cl^- + Bu^tBr \begin{cases} \longrightarrow Bu^tCl + Br^- & (S_N2) \\ \longrightarrow C_4H_8 + H^+ + Br^- + Cl^- & (E1) \end{cases}$$

We have followed the progress of both these reactions by measurement of both bromide ion and hydrogen ion. Complications due to the reversibility of both processes affect mainly the later part of the total change, and have been studied qualitatively. The bimolecular substitution is reversible, but so slightly so that, if it were alone, one could neglect reversibility. However, as we know from the cited investigation of the unimolecular elimination in nitromethane, this reaction also is reversible, and will become more strongly reversed, as, on account of both the concurrent processes, a concentration of bromide ions is built up, so that the acid formed by elimination becomes progressively poorer in hydrogen chloride and richer in the better additive reagent, hydrogen bromide. In our acetone solvent, the effect of this growing reversibility of the elimination is to produce a progressive diversion of the total reaction from elimination towards substitution. Meanwhile, the elimination becomes retarded by its increasing reversibility, until eventually it begins to go backward, thus allowing the concurrent substitution to go further forward. Interested as we were in the rate of the forward process of substitution, we noted these points qualitatively, and then confined our quantitative treatment of the measurements to the first 30—40% of reaction, a range over which the specific rate of development of bromide ion $(dx/dt)/(a - x)$, falls linearly with the decreasing concentration of chloride ion $(b - x)$, thus showing that reversibility has not yet become important. Over this range, the specific rate is simply the sum of a constant part, k_1, the rate constant of reaction $E1$, and a variable part $k_2(b - x)$, which contains the rate-constant k_2 of reaction S_N2.

Tables 1—3 record specimen runs. They illustrate the extent to which the reactions are substitutions, and the applicability to these substitutions of the second-order rate law. Table 4 summarises the second-order rate-constants for the substitutions.

* It is shown in Part XLVII, that for bromine–iodine exchange by Finkelstein substitution, LiBr + RI $\rightleftharpoons$ LiI + RBr, the equilibrium constant k = [LiI][RBr]/[LiBr][RI] in acetone when R is a methyl group is only 1·7, but that for ethyl and higher primary alkyl groups the constants are in the neighbourhood of 7, whilst for the *iso*propyl group the constant is about 30, and for the *tert.*-butyl it is of the order of 100. In the corresponding chlorine–bromine system, LiCl + RBr $\rightleftharpoons$ LiBr + RCl, the equilibrium constants are probably all higher, though the only figure available to illustrate this suggestion is one determined by Dr. P. B. D. de la Mare for the methyl group: for K = [LiBr][MeCl]/[LiCl][MeBr] in acetone at 40°, he found the value 17·5 ± 1·3. In this work, we did not determine them, but ascertained that all are high.

TABLE 1. *Reaction of lithium chloride with methyl bromide in acetone at* 34·04°.

(Initially, [MeBr] = 0·1343, [LiCl] = 0·0503M. Concns. in c.c. of 0·0550N-$AgNO_3$ for 7·55-c.c. sample. Rate constants k_2 in sec.$^{-1}$ mole^{-1} l. The correction to [Br^-] is for mechanical loss, as estimated from the defect of [Cl^- + Br^-] below the theoretical value, 6·90 c.c.—see Experimental section.)

t (sec.)	[Br^-]	[Br^-] (corr.)	[Br^- + Cl^-]	10^2k_2 (uncorr.)	t (sec.)	[Br^-]	[Br^-] (corr.)	[Br^- + Cl^-]	10^2k_2 (uncorr.)
0	0·38	0·39	6·82	—	255	2·25	2·26	6·86	1·30
65	0·59	0·60	6·82	1·26	315	2·54	2·57	6·82	1·23
90	0·83	0·84	6·80	1·22	375	2·86	2·89	6·83	1·21
100	1·95	0·95	6·88	1·26	420	3·03	3·11	6·72	1·20
135	1·16	1·18	6·76	1·26	660	4·05	4·09	6·83	1·18
195	1·72	1·76	6·76	1·25					

(Adopted 10^2k_2, uncorr. = 1·26. Corr. for thermal expansion of the solvent, 10^2k_2 = 1·29.)

TABLE 2. *Reaction of lithium chloride with* iso*propyl bromide in acetone at* 79·63°.

(Initially, [Pr^iBr] = 0·1217; [LiCl] = 0·0721M. Units as in Table 1 unless otherwise noted. Theoretical value of [Br^- + Cl^-] = 9·91 c.c.).

t (min.)	[Br^-]	[Br^-] (corr.)	[Br^- + Cl^-]	10^4k_2	t (min.)	[Br^-]	[Br^-] (corr.)	[Br^- + Cl^-]	10^4k_2
0	1·03	1·06	9·62	—	360	4·00	4·03	9·84	2·23
125	1·92	1·92	9·91	(2·35)	410	4·35	4·35	9·92	2·20
180	2·40	2·47	9·65	2·21	480	4·59	4·71	9·66	2·23
225	2·81	2·85	9·77	2·13	515	4·93	4·99	9·80	2·20
250	3·09	3·13	9·79	2·20	600	5·32	5·43	9·71	2·20
290	3·40	3·46	9·74	2·19	1050	6·65	6·78	9·64	(1·97)

(Adopted 10^4k_2: uncorr., 2·20; corr. for thermal expansion, 2·42.)

TABLE 3. *Reaction of lithium chloride with* tert.*-butyl bromide in acetone at* 55·20°.

(Initially, [Bu^tBr] = 0·1191; [LiCl] 0·0634M. $AgNO_3$, 0·0632N; NaOEt, 0·0222N. Units as in Table 1, unless otherwise stated. Acid concentrations are converted into units used for halide ions.)

t (hr.)	[H^+]	[Br^-] (corr.)	[Br^- + Cl^- − H^+]	$\{(dx/dt)/(a-x)\}$(hr.$^{-1}$)	$(b-x)$ (M)
3·25	0·67	1·20	7·40	0·0232	0·0583
7·0	1·53	2·21	7·59	0·0204	0·0499
11·0	2·07	3·37	7·34	0·0192	0·0402
14·5	2·47	3·98	7·51	0·0168	0·0351
21·75	3·09	5·20	7·53	0·0143	0·0249
24·0	3·14	5·44	7·38	0·0131	0·0231
28·0	3·39	5·89	7·33	0·0119	0·0191
38·75	3·17	6·70	7·33	0·0066	0·0123

(From graph of $(dx/dt)/(a-x)$ against $(b-x)$, 10^5k_2, uncorr. = 0·72, and, corr. for thermal expansion, = 0·76.)

TABLE 4. *Second-order rate constants for reactions of substitution between lithium chloride and alkyl bromides in dry acetone.*

(Initially, [RBr] ~ 0·12M throughout, [LiCl] ~ 0·05M for the reactions of methyl bromide, and ~0·07M for the reactions of the other alkyl bromides. Rate constants, k_2, in sec.$^{-1}$ mole^{-1} l., are tabulated as 10^5k_2. *neo*Pe = *neo*pentyl.)

Temp. (c)	R in RBr:	Me	Et	Pr^n	Pr^i	Bu^i	Bu^t	*neo*Pe
129·82°		—	—	—	—	—	—	3·47
120·04		—	—	—	—	—	—	1·74
109·82		—	—	—	—	—	—	0·851
100·54		—	—	—	—	—	—	0·425
79·63		—	—	—	24·2	—	—	—
64·83		—	314	215	7·96	—	1·94	—
55·20		—	150	106	3·49	28·7	0·76	—
45·19		—	61·7	—	1·42	—	—	—
44·50		—	—	41·0	—	10·4	0·27	—
34·62		—	24·3	16·4	0·522	4·08	—	—
34·04		1290	—	—	—	—	—	—
25·00		—	9·88	6·45	—	1·53	—	—
24·85		592	—	—	—	—	—	—
11·98		175	—	—	—	—	—	—
0·00		52·0	—	—	—	—	—	—

In Table 5, the absolute and the relative rates of the various substitutions at a common temperature are given: the rates are either as measured, or as computed from results for other temperatures. The data give good Arrhenius plots, from which frequency factors

TABLE 5. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), relative rates at common temperatures, and parameters of the equation $k_2 = B_2 \exp(-E_A/RT)$ (with B_2 in sec.$^{-1}$ mole^{-1} l., and E_A in kcal. mole^{-1}) for the reactions of lithium chloride with alkyl bromides in acetone.*

R in RBr:	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
$10^5 k_2$ (25°)	600	9·88	0·13	0·029	6·45	1·53	0·00026
Rel. k_2 (25°)	61	1	0·013	0·0029	0·65	0·15	0·000026
$\log_{10} B_2$	9·3	8·9	7·9	8·9	8·6	8·4	7·4
E_A	15·7	17·6	18·8	21·0	17·5	18·1	21·7

and activation energies have been derived, which are included in Table 5. Discussion of the figures is reserved for Part XLIX.

EXPERIMENTAL

*neo*Pentyl bromide was prepared as described by Sommer, Blankman, and Miller (*J. Amer. Chem. Soc.*, **1951**, **73**, 3542). *iso*Butyl bromide was freed from traces of *tert.*-butyl bromide by shaking it with water until the latter remained neutral to litmus, and was then dried with phosphoric oxide. These and all the other dried alkyl bromides were finally fractionated with a high reflux ratio through a metal-gauze-packed column. The physical constants were as follows: MeBr, b. p. 3·5°/760 mm.; EtBr, b. p. 38·1—38·4°/763 mm.; Pr^{n}Br, b. p. 71·7—72·1°/760 mm.; 72·1—72·4°/765 mm.; Pr^{i}Br, b. p. 59·1—59·5°/760 mm.; Bu^{i}Br, b. p. 90·0—91·0°/763 mm.; Bu^{t}Br, b. p. 72·8—73·0°/758 mm.; *neo*PeBr, b. p. 105·8—106·0°/767 mm.; n_D^{20} 1·4365, n_D^{25} 1·4339. Acetone was purified as described in the preceding paper. Lithium chloride was purified, and reduced to a finely divided form, by filtering its solution in acetone into benzene, and drying the precipitated material in a vacuum at 110° over phosphoric oxide.

Because of the wide range of temperature used, the sealed-tube method was found most convenient for the kinetic work. The tubes were filled with the aid of two automatic pipettes, one delivering an acetone solution of the alkyl bromide, and the other one of lithium chloride. The alkyl bromide solutions were prepared by weighing: for volatile halides, sealed ampoules of them, weighed before and after filling, were broken under the cooled solvent. The lithium chloride solution was also prepared by weighing; and its composition was checked by determination of chloride ion by electrometric titration with silver nitrate. The bulbs of the automatic pipettes were jacketed, so that after they had been charged, their contents could be cooled, before delivery into the reaction tube, if the rate of the reaction studied rendered this precaution necessary. After being charged with both reactants, the tubes were sealed, in such a way as to include as little free space as was safe, and were then kept at −80°, until the whole set, needed for a run, was ready. In order to start a run, the tubes were simultaneously put into the thermostat, and shaken for 1—2 min. Then two or three tubes were withdrawn, at what was to be the time-zero, for the analysis which was to give the composition at zero time; and at later times other tubes were withdrawn and their contents were analysed.

For analysis, a tube was cooled, and its contents were evaporated by rapid pumping. The residual salt was dissolved in water, and analysed for bromide ion, and for total halide ion, by electrometric titration with silver nitrate, in the presence of 5% of barium nitrate, which was added to reduce co-precipitation of the silver halides. The use of the determination of total halide ions is not only that it gave warning of any reaction other than the replacement of one halogen by another in the alkyl halide, but also that it controlled any mechanical loss of salt by the pumping. Such loss showed as a defect in the measured total halide below the halide initially introduced as lithium chloride. Mechanical losses were often in the neighbourhood of 1—2%. For each tube analysed, the estimate thus obtained of the mechanical loss was used to correct the measured content of bromide ion.

Acid was developed in the reactions of *tert.*-butyl bromide, and it was neutralised by titration with ethyl alcoholic sodium ethoxide, with the use of lacmoid as indicator, before the sample was evaporated in preparation for the halide ion analysis.

For all reactions except those of *tert.*-butyl bromide, rate constants were calculated from the equation $k_2 = [2{\cdot}303/t(a-b)] \log_{10} [b(a-x)/a(b-x)]$. The presence of concurrent processes

of different order in the reactions of *tert.*-butyl bromide necessitated a graphical method. In these cases, values of dx/dt were read from the graph of x against t, and then a graph of $(dx/dt)/(a-x)$ against $(b-x)$ was plotted, from the initial steady slope of which k_2 was obtained. All second-order rate-constants were corrected for thermal expansion of the solvent.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLIV. Kinetics of the Interaction of Iodide Ions with Simple Alkyl Chlorides in Acetone.*

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[Reprint Order No. 6208.]

Kinetic experiments on the second-order reactions of halogen substitution by lithium iodide with six simple alkyl bromides in acetone are reported. The reactions are only slightly reversible; but, owing to the use of non-neighbouring halogens, and the circumstance that the salt effect is more negative with higher halide ions, they are subject to a considerable salt disturbance, which was buffered with added lithium perchlorate. In these conditions, rate-constants and the parameters of the Arrhenius equation were determined.

THE pioneer work of Conant and his collaborators on the kinetics of Finkelstein substitutions was concerned with the reaction of iodide ions with alkyl chlorides (Conant and Kirner, *J. Amer. Chem. Soc.*, **1924**, **46**, 232; Conant and Hussey, *ibid.*, **1925**, **47**, 476; Conant, Kirner, and Hussey, *ibid.*, p. 488). However, we can recall no previous account of a kinetic investigation of the reverse process, *viz.*, the reaction of chloride ions with alkyl iodides. The present paper describes a systematic study of the kinetics of this reaction.

In particular, the reactions of substitution between lithium chloride and six simple alkyl iodides in dry acetone as solvent have been investigated. The alkyl groups comprise the α- and β-methylated series of branching homologues to the following extent (*neo*Pe = *neo*pentyl):

(α-Series) Me, Et, Pr^{i}. (β-Series) Et, Pr^{n}, Bu^{i}, *neo*Pe. We tried to cover the α-series completely by including the *tert.*-butyl group, but failed because of the complicated and extensive nature of the side reactions.

The forward reaction, $Cl^- + RI \rightleftharpoons RCl + I^-$, was followed by titration of the iodide ion with ceric sulphate, in the presence of acetone which removed the iodine formed, so that the colour could be seen of the indicator, which was added to show the state of oxidation of the cerium ions. The reactions of which the kinetics are here described were found to be pure substitutions: no acid was formed, and the total halide ion in the solution remained constant. However, in the attempt which was made to study the reaction of lithium chloride with *tert.*-butyl iodide, acid and iodine were liberated, as well as iodide ion.

The kinetic forms of the reactions showed that a disturbance was present. As is illustrated in Table 1, rate constants, calculated for the first 30—70% of the reaction from the formula for an irreversible reaction of the second order, fall with the progress of reaction. We thought it unlikely that the fall could be due to the incursion of a reaction of higher order than two, and the fall was of the wrong form to be ascribed to reversibility.

Our explanation of the drift of the rate constants is that it is a salt effect, despite the constancy of the total concentration. We assume that, like other Finkelstein substitutions, the reactions now studied are subject to a negative salt effect. In solvent acetone, such effects will always be more or less specific to the salts, at the concentrations at which we employ them, and, for lithium chloride and lithium iodide, may be assumed to be different enough to cause a notable disturbance to the rate, as one salt becomes replaced by the

* Part XLIII, preceding paper.

other in the course of reaction. The general correctness of this explanation is made very probable by the observation that the addition of lithium perchlorate, which takes no part in the stoicheiometric reaction, causes a marked general lowering of the rate, and also a disappearance of the drift.

TABLE 1. *Illustration of kinetic forms of reactions of lithium chloride with alkyl iodides in dry acetone.*

{Reaction progress is given in two forms, *viz.*, as the lithium chloride equivalent of the liberated iodide ion, expressed (*A*) as a percentage of the lithium chloride present initially, and (*B*) as a percentage of that present at the time zero. Measure (*A*) gives the composition of the salts present, while measure (*B*) is more closely related to the rate constants k_2, in sec.$^{-1}$ mole^{-1} l., which are computed from the formula

$$k_2 = [2{\cdot}303/t(a-b)] \log_{10} [b(a-x)/a(b-x)]$$

and are corrected for thermal expansion of the solvent.}

Methyl Iodide at 24·83°.—Initially, [MeI] = 0·06267, [LiCl] = 0·03646; at $t = 0$, [MeI] = 0·05721, [LiCl] = 0·03100M. Titres in c.c. of ceric sulphate of 0·00519N-iodide equivalent per 4·236-c.c. sample.

t (min.)	Titre	Reaction (%) (*A*)	Reaction (%) (*B*)	10^5k_2 (corr.)	t (min.)	Titre	Reaction (%) (*A*)	Reaction (%) (*B*)	10^5k_2 (corr.)
0·0	4·46	15·0	0·0	—	5·0	10·46	35·2	23·7	1710
1·0	6·08	20·4	6·4	1970	7·0	12·96	43·8	33·6	1670
2·0	7·47	25·1	11·9	1900	8·0	13·31	44·8	35·0	1650
3·0	8·55	28·8	16·15	1860	10·0	14·26	48·0	38·7	1480
4·0	9·57	32·0	20·2	1750					

TABLE 2. *Kinetic forms of reactions of lithium chloride with alkyl iodides in dry acetone containing lithium perchlorate.*

(See note at the head of Table 1.)

n-*Propyl Iodide at* 25·00°.—Initially, [Pr^{n}I] = 0·06019, [LiCl] = 0·03170, [$LiClO_4$] = 0·1090M; at $t = 0$, [Pr^{n}I] = 0·05997, [LiCl] = 0·03148M. Titre in c.c. of ceric sulphate of 0·000781N-iodide equivalent per 4·236-c.c. sample.

t (min.)	Titre	Reaction (%) (*A*)	Reaction (%) (*B*)	10^5k_2 (corr.)	t (min.)	Titre	Reaction (%) (*A*)	Reaction (%) (*B*)	10^5k_2 (corr.)
0·0	1·19	0·70	0·00	—	200	27·74	16·3	16·1	24·5
40·0	7·33	4·30	3·60	25·1	255	33·91	19·8	19·75	24·5
65·0	11·18	6·55	5·85	24·6	310	40·02	23·5	22·75	24·8
110	16·43	9·65	8·85	26·2	495	57·84	34·0	33·3	25·1
150	21·78	12·75	12·65	24·1				Mean:	24·6

TABLE 3. *Second-order rate constants for reactions of substitution between lithium chloride and alkyl iodides in dry acetone.*

(Initially, [RI] ~ 0·060—0·065, [LiCl] ~ 0·032, [$LiClO_4$] ~ 0·110M. Rate constants, k_2 in sec.$^{-1}$ mole^{-1} l., expressed as 10^5k_2. *neo*Pe = *neo*pentyl.)

Temp. (c)	R in RI:	Me	Et	Pr^n	Pr^i	Bu^i	*neo*Pe
+120·06°		—	—	—	—	—	4·57
109·97		—	—	—	—	—	2·17
100·54		—	—	—	—	—	1·02
80·04		—	—	—	—	—	0·188
63·98		—	—	—	42·3	56·7	—
55·12		—	—	347	20·3	25·8	—
54·04		—	526	—	—	—	—
45·92		—	—	164	9·69	—	—
45·72		—	275	—	—	—	—
45·32		—	—	—	—	10·4	—
35·36		—	113	—	—	—	—
34·74		—	—	61·1	3·48	—	—
34·59		—	—	—	—	4·16	—
34·21		964	—	—	—	—	—
25·64		—	—	—	—	1·71	—
25·23		—	43·0	—	—	—	—
25·00		—	—	24·6	—	—	—
24·83		460	—	—	1·26	—	—
14·45		180	—	—	—	—	—
+14·08		—	14·0	7·83	—	—	—
0·00		37·9	—	—	—	—	—
−9·96		12·9	—	—	—	—	—

We found that by adding a quantity of lithium perchlorate 3—4 times greater than that of the initially present lithium chloride, good rate constants could be calculated by means of the usual equation for an irreversible reaction of the second order, thus confirming that the substitution is indeed of second-order type, and showing incidentally that its reversibility is not sufficiently marked to interfere seriously with the use in this manner of a formula which neglects the retrograde process. These points are illustrated by the examples given in Table 2.

The second-order rate-constants obtained in this way, in the presence of the same constant excess of lithium perchlorate (0·110M), are assembled in Table 3. These rate-constants give satisfactory Arrhenius plots, which lead to the energies of activation and frequency factors shown in Table 4. These figures will be discussed in Part XLIX. Table 4 also contains the absolute and relative rates at a commom temperature for the reactions.

TABLE 4. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), relative rates at a common temperature, and parameters of the equation $k_2 = B_2 \exp(-E_A/RT)$ (with B_2 in sec.$^{-1}$ mole^{-1} l., and E_A in kcal. mole^{-1}) for reactions of lithium chloride with alkyl iodides in acetone containing lithium perchlorate.*

R in RI	Me	Et	Pr^i	Pr^n	Bu^i	*neo*Pe
$10^5 k_2$ (25°)	468	42·0	1·33	24·6	1·62	0·00058
Rel. k_2 (25°)	11·1	1	0·032	0·58	0·038	0·000014
$\log_{10} B_2$	9·4	9·1	8·3	8·8	8·3	7·9
E	16·0	17·0	18·0	17·0	17·8	22·0

EXPERIMENTAL

*neo*Pentyl iodide was prepared by Whitmore and Fleming's method, via *neo*pentane, *neo*pentyl chloride, and *neo*pentyl mercurichloride (*J. Amer. Chem. Soc.*, 1933, **55**, 4161). *iso*Butyl iodide was shaken with aqueous thiosulphate. The other iodides were decoloured with mercury. All the alkyl iodides were finally dried (K_2CO_3) and fractionated: MeI, b. p. 42·4—42·7°/758 mm.; EtI, b. p. 72·2—72·4°/758 mm.; Pr^{n}I, b. p. 101·7—102·1°/760 mm.; Pr^{i}I, b. p. 88·8—89·1°/761 mm.; Bu^{i}I, b. p. 120·0—120·5°/759 mm.; *neo*PeI, b. p. 76—78°/120 mm.

As the analytical method to be used in the kinetic experiments depended on the complete absence of oxidisable impurities in the acetone, this was boiled with permanganate until the colour of the latter persisted, before being distilled with quinol, and dried. Just before use it was redistilled from magnesium perchlorate.

Lithium chloride was purified as indicated in the preceding paper. Lithium perchlorate was prepared by exactly neutralising aqueous lithium hydroxide with perchloric acid, the residue left on subsequent evaporation being dried in a vacuum at 110° over phosphoric oxide.

The sealed-tube method was used for the kinetic runs. The tubes were filled with solutions which were prepared and standardised as described in the preceding paper. Lithium perchlorate, when used, was directly weighed into the acetone, and this solution was employed, instead of the pure solvent, for making up the solutions of lithium chloride and of the alkyl iodide.

Each tube withdrawn from the thermostat, whether at the time-zero or at later times, was broken under 30 c.c. of 2N-aqueous sulphuric acid. The tube contained about 4 c.c. of acetone, but a further 5 c.c. was added, to facilitate rapid absorption of the iodine which was to be produced. Some *o*-phenanthroline–iron(II) indicator was also added. The ceric sulphate titrant, made up in 4N-aqueous sulphuric acid, was standardised with potassium iodide using a like method. With the concentrations of acid and of acetone here given, the end-points were sharp and stable. Control experiments showed that chloride did not appreciably affect the determination of iodide ions by this method. It was also shown, by means of other control experiments, in which the alkyl halides were pumped off before the determination of iodide ions, that the presence of the organic halides does not disturb this determination.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLV. Kinetics of the Interaction of Bromide Ions with Simple Alkyl Bromides in Acetone.*

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Kinetic experiments on the second-order reaction of bromine exchange between lithium radio-bromide and seven simple alkyl bromides in acetone are reported. In the one case of *tert.*-butyl bromide, the bimolecular substitution is accompanied by a probably unimolecular side reaction, in an amount which is too small to show in the kinetics, but is revealed by its component elimination, which produces a trace of acid. All the reactions are subject to a negative salt effect of approximately uniform character. These disturbances being dealt with, rate constants and parameters of the Arrhenius equation are evaluated.

Theoretical discussions of the transition states of Finkelstein substitutions are so much simplified when the forward and retrograde processes become identical, that special interest attaches to the experimental examination of exchange reactions, such as that between lithium radio-bromide and alkyl bromides, in a solvent, such as dry acetone, in which the bimolecular mechanism of substitution prevails over a wide range of alkyl structures:

$$^{*}Br^{-} + RBr \rightleftharpoons RBr^{*} + Br^{-}$$

For a few alkyl bromides rates of this exchange have been measured in the less generally applicable solvents, aqueous acetone, ethylene diacetate, and ethyl alcohol (le Roux, Lu, Sugden, and Thomson, *J.*, 1945, **586**; Miller, Neimen, and Protsenko, *Doklady Akad. Nauk S.S.S.R.*, 1950, **75**, 403; 1951, **77**, 423). The exchange of α-bromopropionic acid has been examined in water, but the results are complicated by hydrolysis (Koskoski, Dodson, and Fowler, *J. Amer. Chem. Soc.*, 1941, **63**, 2149). Rates of the exchange in dry acetone have been measured hitherto only for individual alkyl bromides, each for some special purpose, *i.e.*, 1-phenylethyl bromide and α-bromopropionic acid for the proof of inversion in S_N2 substitutions (Hughes, Juliusberger, Scott, Topley, and Weiss, *J.*, 1936, 1173; Cowdrey, Hughes, Nevell, and Wilson, *J.*, 1938, 209), 1-methylallyl and crotyl bromide, for the establishment of bimolecular (S_N2') anionotropy (England and Hughes, *Nature*, 1951, **168**, 1002), and *n*-butyl and 1-methylheptyl bromide in a study of the kinetic effects of salt concentration on the substitution (Evans and Sugden, *J.*, 1949, 270).

We now record measurements of the rate, in solvent acetone, and in standardised conditions of salt-concentration, of the exchange reaction of lithium radio-bromide with a number of alkyl bromides, chosen to furnish material for a study of the simplest elements of the effect of alkyl structure on the kinetics of this substitution. The alkyl groups were those needed to form the two branching-homologous series, which we call the α- and β-methylated series (see p. 3173). Each substitution has been studied over a range of temperature, and the Arrhenius parameters have been evaluated. The effect of varying the concentrations of the reactants has been examined, with results which will be illustrated; but in the main series of experiments now reported, these concentrations were standardised.

All the substitutions are kinetically of second order, subject to the following qualifications. The first is that the exchange of *tert.*-butyl bromide only is accompanied by a minor side reaction. The second is that all the exchanges are subject to a negative salt effect of an approximately uniform nature. A third kinetic deviation, which can be described as a negative co-solvent effect of the alkyl halides, becomes appreciable only at higher concentrations of alkyl halide than were employed in the measurements now recorded (usually below 0·2M). We discuss the first two of these disturbances before reporting the main results.

The side reaction undergone by *tert.*-butyl bromide could hardly have been detected

* Part XLIV, preceding paper.

simply from the kinetics of the halogen exchange; but it was revealed by the production of a small amount of free acid in the solution. The nature of this side reaction may be inferred from parallel work on the kinetics of halide-ion substitutions of *tert.*-butyl bromide in nitromethane: in this solvent unimolecular reactions are prominent and include elimination (de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930). We know also that 1-mesitylethyl chloride, in which bimolecular substitution is subject to steric hindrance (forthcoming paper), undergoes unimolecular substitution, as measured by the accompanying racemisation, even in dry acetone (Charlton and Hughes, *J.*, 1954, 2939). We conclude that, in dry acetone, *tert.*-butyl bromide, uniquely among the alkyl halides studied, associates with its main reaction of bimolecular substitution, a small amount of unimolecular side-reaction, which we are able to detect by the distinctive stoicheiometry of its component elimination. In order to ascertain to what extent the occurrence of this unimolecular reaction could affect the determined values of the second-order rate constant of substitution, the first main series of experiments on *tert.*-butyl bromide, *i.e.*, the series corresponding exactly to those conducted on all the other alkyl bromides, was paralleled by several other series in which the concentrations of the reactants were so changed as to alter the relative importance of concurrent unimolecular and bimolecular reactions, and thus to alter the magnitude of a disturbance due to the former. Thus in the fourth series (Table 2) the concentration of *tert.*-butyl bromide was approximately halved and that of the lithium bromide doubled, changes that should reduce the disturbance. In the fifth series the concentration of lithium bromide was approximately quadrupled. However, as can be seen from Tables 1 and 2, these changes do not appreciably affect the second-order rate constants, except in the way which is described below as a salt effect and is not peculiar to *tert.*-butyl bromide.

Negative kinetic effects in Finkelstein substitutions have been observed in several solvents and for several salts, including non-interacting salts, as is illustrated in several of the present and forthcoming papers: the physical mechanism of the effect will be discussed in a later paper. Here we are concerned with the problem of so treating the effect of an increased concentration of lithium bromide in reducing the second-order rate constants of its reactions with alkyl bromides, that it will not interfere with the intended kinetic comparison of the alkyl bromides. An illustration of the salt effect, referring to the reactions of *iso*propyl and *tert.*-butyl bromide, is given in Table 1.

TABLE 1. *Relation between second-order rate constants* ($k_2^{(b)}$ *in sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *of reactions between lithium bromide and alkyl bromides in acetone and the concentration* (*b in moles per l.*) *of the lithium bromide.*

The rate values $k_2^{(0\cdot024)}$, corresponding to the " standard " salt concentration 0·024M, are calculated from the equation of the straight line in the Figure, *viz.*, $\log_{10}(k_2^{(b)}/k_2^{(0\cdot024)}) = -0\cdot37\log_{10}(b/0\cdot024)$.

	LiBr + PrⁱBr in Me_2CO at 57·8°			LiBr + BuᵗBr in Me_2CO at 44·4°.		
b	0·0172	0·0231	0·0597	0·0238	0·0474	0·0918
$10^5k_2^{(b)}$ (obs.)	53·0	47·3	36·0	5·20	4·06	3·15
$10^5k_2^{(0\cdot024)}$ (calc.)	47·0	46·8	50·5	5·20	5·22	5·19

Evans and Sugden (*loc. cit.*) examined the salt effect for the corresponding reactions of *n*-butyl and 1-methylheptyl bromide. We have noticed that if for each of their halides and ours, we plot the logarithm of the rate constant against that of the salt concentration, straight lines are obtained of similar slope within the concentration range of 0·001M and 0·1M; and that, therefore, if we re-express the rates for each alkyl halide in terms of the rate for that alkyl halide at a standard salt concentration, a logarithmic plot results in which, as shown in the Figure, all the points lie close to a single straight line. It cannot, of course, have any deep significance that points applying to different alkyl halides reacting at different temperatures should fit the same line; but the observation of such an approximate fit does provide a convenient basis for standardising salt effects in the different reactions to be compared. It also confirms, what we knew on other grounds, *viz.*, that salt effects, when standardised, do not significantly disturb activation energies determined by the Arrhenius equation.

TABLE 2. *Second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of bromine exchange between lithium radio-bromide and alkyl bromides in acetone.*

Temp. (c)	a = [AlkBr]	b = [LiBr]	$t_2 - t_1$ (min.)	Counting rates C	$C - X_1$	$C - X_2$	$10^5 k_2^{(1)}$	$10^5 k_2^{(0\cdot024)}$	Mean
				Methyl bromide.					
−11·0°	0·1614	0·0268	18·4	466·7	469·3	263·1	344 ± 5	354	
,,	0·1667	0·0268	26·1	466·7	469·3	214·8	326 ± 4	336	
,,	0·1716	0·0240	27·5	447·7	432·4	180·4	341 ± 4	341	
,,	0·1714	0·0240	29·9	447·7	432·4	173·6	330 ± 3	330	
,,	0·1763	0·0242	23·7	365·6	344·3	159·7	335 ± 5	336	
,,	0·1517	0·0242	30·2	365·6	344·3	148·9	343 ± 6	344	340
−17·8	0·1644	0·0254	40·0	220·6	197·8	119·5	138 ± 4	140	
,,	0·1843	0·0254	33·7	220·6	197·8	121·4	140 ± 4	142	
,,	0·1637	0·0241	41·8	322·8	305·6	181·9	134 ± 3	134	
,,	0·1710	0·0241	43·7	322·8	305·6	173·4	134 ± 3	135	
,,	0·1715	0·0232	41·1	225·9	220·3	119·1	154 ± 4	153	
,,	0·1662	0·0232	52·3	225·9	220·3	102·0	160 ± 3	159	
,,	0·1668	0·0238	40·1	396·3	384·1	215·8	152 ± 3	152	
,,	0·1753	0·0238	53·3	396·3	384·1	172·0	156 ± 2	156	146
−24·6	0·1650	0·0231	104·4	216·8	207·3	112·7	62·2 ± 1·4	61·6	
,,	0·1575	0·0231	126·5	216·8	207·3	99·4	62·9 ± 1·3	62·3	
,,	0·1827	0·0244	118·5	526·0	533·7	238·9	66·2 ± 0·7	66·4	
,,	0·1713	0·0244	86·8	526·0	533·7	305·8	64·7 ± 0·9	65·0	
,,	0·1669	0·0228	89·0	223·4	231·8	138·7	58·0 ± 1·1	57·2	
,,	0·1836	0·0228	116·3	223·4	231·8	103·0	66·3 ± 0·9	65·5	63·0
−31·0	0·1691	0·0233	135·8	236·0	229·2	160·9	26·6 ± 1·1	25·3	
,,	0·1682	0·0233	158·9	236·0	229·2	156·6	24·6 ± 1·0	24·4	
,,	0·1530	0·0244	140·0	152·8	156·3	109·1	28·0 ± 0·8	28·1	
,,	0·1596	0·0244	172·3	152·8	156·3	98·5	28·5 ± 0·7	28·6	
,,	0·1501	0·0249	121·0	239·3	236·0	176·8	27·3 ± 1·3	27·6	
,,	0·1645	0·0249	127·4	239·3	236·0	170·1	26·8 ± 1·3	27·1	26·8

Temp. (c)	a = [AlkBr]	b = [LiBr]	$10^5 k_2^{(1)}$	$10^5 k_2^{(0\cdot024)}$
		Ethyl bromide		
25·1°	0·1640	0·0242	171 ± 2	171
,,	0·1640	0·0242	163 ± 2	163
,,	0·1639	0·0229	155 ± 3	153
,,	0·1639	0·0229	183 ± 2	181
,,	0·1639	0·0243	178 ± 4	179
,,	0·1639	0·0243	172 ± 3	173
,,	0·1639	0·0243	169 ± 3	169
			Mean	170
16·4	0·1614	0·0240	68·8 ± 1·0	66·8
,,	0·1614	0·0240	66·6 ± 0·8	66·6
,,	0·1614	0·0240	67·8 ± 0·7	67·8
,,	0·1610	0·0242	64·7 ± 1·1	64·9
,,	0·1610	0·0242	64·9 ± 0·9	65·0
			Mean	66·2
7·9	0·1643	0·0247	24·1 ± 0·3	24·3
,,	0·1643	0·0247	25·8 ± 0·3	26·0
,,	0·1660	0·0249	29·5 ± 0·4	29·8
,,	0·1660	0·0249	28·9 ± 0·4	29·1
,,	0·1660	0·0249	28·9 ± 0·4	29·2
,,	0·1663	0·0242	26·8 ± 0·5	26·9
			Mean	27·6
0·0	0·1667	0·0251	11·0 ± 0·1	11·2
,,	0·1667	0·0251	11·2 ± 0·1	11·4
,,	0·1665	0·0249	9·2 ± 0·24	9·3
,,	0·1665	0·0249	8·5 ± 0·23	8·6
,,	0·1629	0·0193	12·3 ± 0·2	11·7
,,	0·1629	0·0193	12·2 ± 0·2	11·6
			Mean	10·6

Temp. (c)	a = [AlkBr]	b = [LiBr]	$10^5 k_2^{(1)}$	$10^5 k_2^{(0\cdot024)}$
		Ethyl bromide		
−10·9°	0·1719	0·0253	3·11 ± 0·11	3·15
,,	0·1719	0·0253	3·02 ± 0·12	3·06
,,	0·1708	0·0245	2·80 ± 0·11	2·81
,,	0·1708	0·0245	2·89 ± 0·11	2·91
,,	0·1681	0·0200	2·79 ± 0·13	2·67
,,	0·1681	0·0200	2·89 ± 0·14	2·76
			Mean	2·89
		n-Propyl bromide		
30·8	0·1607	0·0242	207 ± 4	208
,,	0·1607	0·0242	160 ± 2	160
,,	0·1607	0·0242	203 ± 4	204
,,	0·1614	0·0246	164 ± 3	165
,,	0·1614	0·0246	210 ± 3	211
,,	0·1614	0·0246	204 ± 3	206
,,	0·1616	0·0227	201 ± 4	198
,,	0·1616	0·0227	208 ± 4	205
,,	0·1616	0·0227	167 ± 4	165
			Mean	191
14·9	0·1679	0·0247	42·6 ± 0·6	42·9
,,	0·1679	0·0247	39·0 ± 0·5	39·3
,,	0·1679	0·0247	40·6 ± 0·6	40·9
,,	0·1675	0·0227	40·8 ± 0·9	40·3
,,	0·1675	0·0227	41·3 ± 0·5	40·7
,,	0·1675	0·0227	42·3 ± 0·5	41·7
			Mean	41·0

TABLE 2. (*Continued.*)

Temp. (c)	*a* = [AlkBr]	*b* = [LiBr]	$10^5k_2^{(5)}$	$10^5k_2^{(0\cdot024)}$
			n-*Propyl bromide*	
−6·6°	0·1627	0·0283	2·91 ± 0·06	3·04
,,	0·1627	0·0283	3·16 ± 0·06	3·30
,,	0·1644	0·0258	3·42 ± 0·10	3·48
,,	0·1644	0·0258	3·23 ± 0·10	3·29
,,	0·1644	0·0258	3·31 ± 0·10	3·37
			Mean	3·30
			iso-*Propyl bromide*	
65·3	0·1549	0·0226	83·6 ± 2·8	82·4
,,	0·1549	0·0226	98·5 ± 2·1	97·0
,,	0·1552	0·0222	99·2 ± 2·0	97·3
,,	0·1552	0·0212	98·4 ± 1·5	96·5
,,	0·1573	0·0227	102·0 ± 2·4	100
,,	0·1573	0·0227	99·8 ± 1·0	97·4
			Mean	95·1
57·8	0·1588	0·0222	50·0 ± 0·9	49·0
,,	0·1588	0·0222	46·9 ± 0·7	46·0
,,	0·1587	0·0207	49·5 ± 1·2	47·5
,,	0·1587	0·0207	49·0 ± 0·9	47·3
,,	0·1565	0·0263	44·9 ± 1·4	46·0
,,	0·1565	0·0263	43·6 ± 1·1	44·7
			Mean	46·7
50·0	0·1490	0·0235	27·1 ± 0·6	26·9
,,	0·1490	0·0235	23·8 ± 0·5	23·6
,,	0·1562	0·0235	24·4 ± 0·7	24·3
,,	0·1562	0·0235	24·3 ± 0·6	24·2
,,	0·1565	0·0238	24·6 ± 0·4	24·6
,,	0·1565	0·0238	24·1 ± 0·3	24·1
			Mean	24·6
42·0	0·1555	0·0242	11·3 ± 0·2	11·3
,,	0·1555	0·0242	10·1 ± 0·2	10·1
,,	0·1608	0·0231	9·7 ± 0·2	9·8
,,	0·1608	0·0231	10·5 ± 0·2	10·4
,,	0·1630	0·0244	10·8 ± 0·3	10·8
,,	0·1630	0·0244	10·9 ± 0·3	10·9
			Mean	10·5
34·9	0·1594	0·0232	5·05 ± 0·14	5·00
,,	0·1594	0·0232	5·21 ± 0·12	5·17
,,	0·1655	0·0257	5·33 ± 0·18	5·43
,,	0·1655	0·0257	5·01 ± 0·17	5·10
,,	0·1622	0·0245	4·98 ± 0·23	5·01
,,	0·1622	0·0245	4·70 ± 0·22	4·73
			Mean	5·07
			iso-*Propyl bromide* (2*nd series*)	
57·8	0·1597	0·0172	53·0 ± 0·3	—
,,	0·1597	0·0172	53·1 ± 1·2	—
			iso-*Propyl bromide* (3*rd Series*)	
57·8	0·1650	0·0597	34·7 ± 1·3	—
,,	0·1650	0·0597	37·2 ± 1·0	—
			iso-*Butyl bromide*	
57·8	0·1564	0·0237	149 ± 7	149
,,	0·1564	0·0237	155 ± 6	155
,,	0·1564	0·0237	160 ± 6	159
,,	0·1605	0·0243	141 ± 6	141
,,	0·1605	0·0243	128 ± 5	128
,,	0·1605	0·0243	134 ± 5	134
			Mean	144
50·0	0·1600	0·0194	79·6 ± 2·2	75·7
,,	0·1600	0·0194	78·1 ± 2·1	74·2
,,	0·1600	0·0194	74·6 ± 1·7	70·9
,,	0·1608	0·0264	68·6 ± 3·0	70·3
,,	0·1608	0·0264	65·3 ± 2·2	67·0
,,	0·1608	0·0264	60·9 ± 1·8	64·2
			Mean	70·4

Temp. (c)	*a* = [AlkBr]	*b* = [LiBr]	$10^5k_2^{(5)}$	$10^5k_2^{(0\cdot024)}$
			iso-*Butyl bromide*	
41·8°	0·1637	0·0242	35·7 ± 0·6	35·8
,,	0·1637	0·0242	35·7 ± 0·7	35·8
,,	0·1637	0·0242	36·2 ± 0·7	36·3
,,	0·1641	0·0214	35·9 ± 1·2	34·9
,,	0·1641	0·0214	34·1 ± 0·9	33·1
,,	0·1641	0·0214	30·5 ± 0·8	29·7
			Mean	34·3
32·8	0·1651	0·0261	13·6 ± 0·6	13·9
,,	0·1651	0·0261	13·3 ± 0·5	13·6
,,	0·1651	0·0261	13·4 ± 0·4	13·7
,,	0·1435	0·0236	14·6 ± 0·3	14·5
,,	0·1435	0·0236	14·7 ± 0·2	14·6
,,	0·1435	0·0236	13·5 ± 0·2	13·5
			Mean	14·0
25·1	0·1670	0·0229	6·20 ± 0·20	6·12
,,	0·1670	0·0229	6·67 ± 0·20	6·59
,,	0·1670	0·0229	6·28 ± 0·16	6·20
,,	0·1693	0·0232	6·46 ± 0·10	5·41
,,	0·1693	0·0232	6·62 ± 0·11	6·56
,,	0·1693	0·0232	4·90 ± 0·08	4·86
,,	0·1652	0·0237	5·82 ± 0·10	5·80
,,	0·1652	0·0237	5·92 ± 0·09	5·90
,,	0·1652	0·0237	5·50 ± 0·09	4·98
			Mean	5·82
			tert.-*Butyl bromide*	
79·1	0·1619	0·0238	121 ± 11	121
,,	0·1619	0·0238	151 ± 14	150
,,	0·1598	0·0236	160 ± 7	159
,,	0·1598	0·0236	152 ± 4	151
,,	0·1584	0·0228	145 ± 5	143
,,	0·1584	0·0228	154 ± 3	152
			Mean	146
70·6	0·1645	0·0260	71·3 ± 0·7	72·8
,,	0·1645	0·0260	73·0 ± 2·1	74·5
,,	0·1614	0·0234	71·3 ± 3·6	70·8
,,	0·1614	0·0224	76·5 ± 2·2	75·2
,,	0·1614	0·0224	75·6 ± 1·9	74·2
			Mean	73·5
60·2	0·1680	0·0225	22·3 ± 0·5	21·9
,,	0·1644	0·0220	28·0 ± 0·9	27·4
,,	0·1644	0·0220	27·4 ± 1·9	26·8
,,	0·1637	0·0216	27·3 ± 0·7	26·6
,,	0·1637	0·0216	26·9 ± 0·6	26·2
			Mean	25·8
49·4	0·1666	0·0236	8·55 ± 0·15	8·51
,,	0·1666	0·0236	8·33 ± 0·17	8·29
,,	0·1655	0·0232	8·38 ± 0·19	8·30
,,	0·1655	0·0232	8·48 ± 0·18	8·41
,,	0·1655	0·0232	8·57 ± 0·18	8·50
,,	0·1655	0·0232	8·83 ± 0·18	8·76
			Mean	8·46
40·0	0·1697	0·0335	2·79 ± 0·19	3·06
,,	0·1697	0·0335	2·59 ± 0·18	2·84
,,	0·1689	0·0191	3·48 ± 0·44	3·29
,,	0·1689	0·0191	3·28 ± 0·22	3·11
,,	0·1689	0·0191	3·00 ± 0·24	2·84
			Mean	3·03
25·1	0·1657	0·0258	0·543 ± 0·016	0·544
,,	0·1657	0·0258	0·485 ± 0·016	0·494
,,	0·1657	0·0258	0·508 ± 0·015	0·518
,,	0·1655	0·0229	0·553 ± 0·013	0·546
,,	0·1655	0·0229	0·535 ± 0·014	0·529
			Mean	0·526

TABLE 2. (*Continued.*)

Temp. (c)	a = [AlkBr]	b = [LiBr]	$10^5k_2^{(5)}$	$10^5k_2^{(0\cdot024)}$
	tert.-*Butyl bromide* (2nd series)			
44·4°	0·0720	0·0238	5·33 ± 0·024	5·32
,,	0·0720	0·0238	5·39 ± 0·026	5·37
,,	0·0720	0·0238	4·90 ± 0·027	4·89
			Mean	5·19
	tert.-*Butyl bromide* (3rd series)			$10^5k_2^{(0\cdot050)}$
44·4	0·1440	0·0477	3·94 ± 0·09	3·88
,,	0·1440	0·0477	3·97 ± 0·09	3·90
,,	0·1440	0·0477	4·08 ± 0·09	4·01
			Mean	3·93
	tert.-*Butyl bromide* (4th series)			
59·8	0·0700	0·0477	16·1 ± 0·8	15·8
,,	0·0700	0·0477	20·9 ± 0·6	20·6
,,	0·0714	0·0441	20·3 ± 0·5	19·4
,,	0·0714	0·0441	20·6 ± 0·5	19·7
,,	0·0686	0·0479	21·1 ± 0·9	20·8
,,	0·0686	0·0479	17·7 ± 0·8	17·5
,,	0·0686	0·0479	20·4 ± 0·8	20·1
			Mean	19·1
44·4	0·0751	0·0474	4·25 ± 0·13	4·17
,,	0·0751	0·0474	3·97 ± 0·10	3·89
,,	0·0751	0·0474	3·97 ± 0·12	3·90
			Mean	3·99
35·0	0·0834	0·0534	1·40 ± 0·05	1·43
,,	0·0834	0·0534	1·52 ± 0·05	1·55
,,	0·0834	0·0534	1·49 ± 0·05	1·52
			Mean	1·50
25·1	0·0738	0·0567	0·409 ± 0·020	0·429
,,	0·0738	0·0567	0·400 ± 0·021	0·420
,,	0·0738	0·0567	0·354 ± 0·020	0·371
,,	0·0822	0·0493	0·416 ± 0·021	0·413
,,	0·0822	0·0493	0·457 ± 0·022	0·455
,,	0·0724	0·0472	0·334 ± 0·016	0·328
,,	0·0724	0·0472	0·433 ± 0·019	0·424
			Mean	0·406

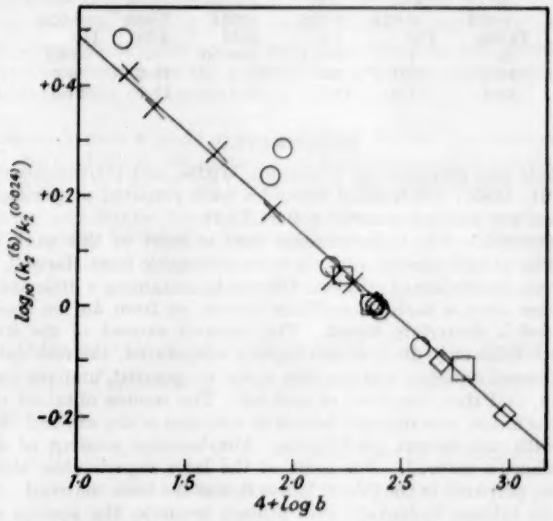
Temp. (c)	a = [AlkBr]	b = [LiBr]	$10^5k_2^{(5)}$	$10^5k_2^{(0\cdot024)}$
	tert.-*Butyl bromide* (5th series)			
44·4°	0·0759	0·0918	3·50 ± 0·20	—
,,	0·0759	0·0918	2·98 ± 0·21	—
,,	0·0759	0·0918	2·97 ± 0·20	—
	neo*Pentyl bromide*			
135·2	0·1534	0·0274	55·7 ± 1·1	57·7
,,	0·1534	0·0274	55·4 ± 1·4	57·4
,,	0·1552	0·0225	58·9 ± 1·5	57·9
,,	0·1552	0·0225	63·4 ± 1·2	62·4
,,	0·1553	0·0230	56·8 ± 2·1	56·2
,,	0·1553	0·0230	62·5 ± 1·6	61·8
			Mean	58·9
123·7	0·1662	0·0184	29·7 ± 0·8	27·9
,,	0·1662	0·0184	31·7 ± 1·0	29·8
,,	0·1601	0·0235	30·0 ± 0·8	29·8
,,	0·1601	0·0235	30·2 ± 0·6	30·0
,,	0·1570	0·0241	25·6 ± 0·8	25·6
,,	0·1570	0·0241	24·8 ± 0·5	24·9
			Mean	28·0
116·1	0·1624	0·0236	16·0 ± 0·6	16·0
,,	0·1624	0·0236	17·2 ± 0·6	17·1
,,	0·1678	0·0244	15·4 ± 0·5	15·5
,,	0·1678	0·0244	15·4 ± 0·5	15·4
,,	0·1583	0·0239	16·8 ± 0·6	16·8
,,	0·1583	0·0239	15·9 ± 0·6	15·8
			Mean	16·1
105·3	0·1652	0·0237	6·40 ± 0·50	6·38
,,	0·1652	0·0237	7·24 ± 0·51	7·21
,,	0·1633	0·0239	6·49 ± 0·51	6·48
,,	0·1633	0·0239	7·27 ± 0·45	7·27
,,	0·1615	0·0244	7·23 ± 0·48	7·26
,,	0·1615	0·0244	7·94 ± 0·39	7·97
			Mean	7·10
88·6	0·1669	0·0236	1·86 ± 0·04	1·85
,,	0·1669	0·0236	2·10 ± 0·05	2·10
,,	0·1669	0·0236	1·80 ± 0·03	1·79
,,	0·1669	0·0236	1·80 ± 0·03	1·79
,,	0·1650	0·0267	1·78 ± 0·08	1·83
,,	0·1650	0·0267	1·80 ± 0·07	1·84
,,	0·1650	0·0267	1·93 ± 0·07	1·99
			Mean	1·88

Our procedure has been to correct, to a standard salt concentration, rates measured at concentrations not far from the standard. If the relation, illustrated in the Figure, were absolute, we could, for any alkyl halide, compute the rate of its reaction at the standard concentration from measurements made at any concentration: the degree of success of such calculations, when considerable concentration differences are involved, can be judged from the degree of constancy of the values in the last line in Table 1. However, we have used the relation for computing only those small corrections to the rate which arise from the small deviations of experimental concentrations from a standard value.

The main groups of experiments are recorded in Table 2. The measurements refer to the losses of radioactivity of lithium bromide after periods of time in which it exchanges its active halogen for inactive halogen from the alkyl bromides. The counting rates C, $C - X_1$, and $C - X_2$ mean respectively specific activities of inorganic halide initially, on separation at a time t_1 soon after the reaction solution has attained thermostat temperature, and on separation at some later time t_2. But, because the radioactivity, which in general depended on the presence of both ^{80}Br and ^{82}Br, was short-lived, the figures given had to be derived in a slightly more involved way than applies to those of the chlorine exchange studied in Part XLII. When a sample taken at t_2 was to be counted, a sample taken at t_1, and an initial sample, were also counted, and these counts were repeated, more

than once if necessary, so that curves could be drawn which overlapped in time, showing, for each sample, the logarithmic fall in the counting rate with time. From the curves, counts at a common time could be read, which were then converted into specific counting rates, after determining, by Volhard's method, the bromide-ion contents of the solutions counted. Comparison of the counts C and $C - X_1$ indicates the amounts of reaction, in many cases negligible, which take place during the period of warming to thermostat temperature. The second-order rate constants, $k_2^{(b)}$, computed from the counting rates, are corrected for thermal expansion of the solvent. The main error in these values is due to the random fluctuations of finite counts. This error is measured statistically by probable errors computed from the magnitudes of the individual counts, and is expressed in Table 2

Representation of kinetic salt effects in reactions of lithium bromide with four alkyl bromides in acetone.



× *n*-Butyl bromide at 26·2° ..... } Evans and Sugden (*loc. cit.*).
○ 1-Methylheptyl bromide at 65·3° ..... }
□ *iso*-Propyl bromide at 57·6° ..... } Table 1
◊ *tert.*-Butyl bromide at 44·4° ..... }

The equation of the straight line is

$$\log_{10} (k_2^{(b)}/k_2^{(0\cdot024)}) = -0\cdot37 \log_{10} (b/0\cdot024).$$

in the form of probable errors in the derived individual rate constants. In the last two columns of Table 2, the individual and averaged rate constants are corrected, as already described, to the standard salt concentration, which was 0·024M, except in some of the supplementary series of runs carried out with *tert.*-butyl bromide.

In these supplementary series, the main purpose of which was to check, by varying the concentrations of the reactants, the possibility of measurable error through the incursion of unimolecular reactions, the opportunity was taken to examine whether the radioactivity in the lithium bromide, separated after a period of reaction, is noticeably disturbed by the very small amount of hydrogen bromide formed. To this end, the initial count C of the lithium bromide was remeasured, in association with counts on samples of the reaction solution after various periods of reaction, in a modified form, C', which involved, first, mixing the original lithium bromide solution with a sample of a *tert.*-butyl bromide solution which had been heated in the thermostat for the same length of time as the reaction solution, then separating the lithium bromide by the procedure used for the reaction solution, and

then carrying through the count. In fact, the counts C, C', and $C - X_1$, were all substantially identical, as is illustrated in Table 2 with respect to the counts C' and $C - X_1$ in the runs in which this modified procedure was adopted.

The mean rate constants at standard salt concentration give good Arrhenius plots, from which frequency factors and energies of activation have been derived, as entered in Table 3, which also contains the absolute and relative rates interpolated or extrapolated to 25°. Discussion of the figures is reserved for Part XLIX.

TABLE 3. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), relative rates at common temperatures, and parameters of the equation $k_2 = B_2 \exp(-E_A/\boldsymbol{R}T)$ (with B_2 in sec.$^{-1}$ mole^{-1} l. and E_A in kcal. mole^{-1}) for the reactions of lithium radio-bromide with alkyl bromides in acetone.*

R in RBr	Me	Et	Pr^i	Bu^s		Pr^n	Bu^i	*neo*Pe
b	0·024	0·024	0·024	0·024	0·050	0·024	0·024	0·024
$10^5 k_2$ (25°)	13,000	170	1·8	0·51	0·38	110	5·7	0·0026
Rel. k_2 (25°)	76	1	0·011	0·0030	—	0·65	0·033	0·000015
$\log_{10} B_2$	10·7	10·1	9·7	10·7	10·5	9·8	9·6	8·6
E_A	15·8	17·5	19·7	21·8	21·7	17·5	18·9	22·0

EXPERIMENTAL

*neo*Pentyl bromide was prepared by Whitmore, Wittle, and Harriman's method (*J. Amer. Chem. Soc.*, 1939, **61**, 1585); other alkyl bromides were prepared or purified as described in Part XLIII; acetone was purified as noted in Part XLII.

Lithium Radio-bromide.—The radio-bromine used in most of this work, which was done before supplies of ^{82}Br of high specific activity were obtainable from Harwell, was made in the laboratory by neutron-irradiation of ethylene dibromide containing a little aniline, the neutrons being obtained either from a radium-beryllium source, or from an ion-accelerator in which deuterons bombarded a deuterium target. The aqueous extract of the irradiated material was neutralised with lithium hydroxide and rapidly evaporated, the residual lithium bromide being fused. Its filtered aqueous solution was again evaporated, and the residue was heated until melting began, and then dissolved in acetone. The residue obtained on evaporation of the filtered acetone solution, was strongly heated in a current of dry air, and dissolved in acetone previously dried with magnesium perchlorate. The bromide content of this solution was determined by Volhard's method. For some of the later experiments, strongly radioactive ammonium bromide, prepared in the pile at Harwell, was the basic material. It was converted, by evaporation with lithium hydroxide, into lithium bromide, the acetone solution of which was suitably diluted with one of ordinary lithium bromide.

Kinetics.—For the four less reactive alkyl bromides, *iso*propyl, *iso*butyl, *tert.*-butyl, and *neo*pentyl bromide, the sealed-tube method was employed; the tubes were charged and the runs started as described in Part XLIII. In the cases of the more reactive ethyl and *n*-propyl bromide, the solutions of alkyl halide and of lithium bromide were placed in the limbs of inverted Y-tubes, which were sealed, and allowed to reach thermostat temperature; then the solutions were mixed by tilting. The volatility and high reactivity of methyl bromide necessitated enclosing it in small sealed ampoules within the reaction tubes, which contained acetone solutions of lithium bromide, the inner ampoules being broken by shaking after the tube and all its contents had been cooled to −80°.

The runs with ethyl, *n*-propyl, *iso*propyl, *iso*butyl, and *neo*pentyl bromides were stopped by cooling a tube, transferring its contents to a flask, and evaporating the volatile material by pumping. The residue, after re-evaporation with fresh acetone, was dissolved in water for counting. That no appreciable reaction accompanies this procedure, is shown by comparison of the counts C and $C - X_1$, which would include any such reaction in the estimate which it gives of the reaction accompanying warming to thermostat temperature, with the result that, if reaction during working-up were appreciable, the difference between C and $C - X_1$ would not become negligible, as in fact it does, at the lower temperatures used with each alkyl bromide. Methyl bromide reacted too rapidly to allow the use of this technique: runs with this halide were stopped by pouring the reaction solution into a mixture of benzene and water, washing the benzene extract with water, and extracting the combined aqueous solutions with benzene, and evaporating the aqueous solutions to dryness, the residue being dissolved in water for counting. For *neo*pentyl bromide a similar method was used, but with ether instead of benzene

as the organic solvent, the main reason in this case being that it was desired to recover the alkyl halide.

Counting.—All counts were made with aqueous solutions in the same counting tube. Among the checks applied was one for the proportionality of the counting rate to the concentration of radioactive material, by the counting of a solution of lithium radio-bromide in which the ^{80}Br had decayed and only the ^{82}Br was active, in five successive degrees of two-fold dilution. In general the logarithmic decay curve of the lithium radio-bromide employed was not linear owing to the simultaneous presence of both radio-isotopes; but it became linear as the shorter-lived ^{80}Br decayed. The principle of taking counts comparatively on two or more solutions during overlapping time-intervals, and of thus allowing for radioactive decay, has been explained, as well as the method of converting such counts to the specific counting rates, C, C', $C - X_1$, and $C - X_2$ (p. 3171). The other quantities required for the calculation of rate constants are a, based on direct weighing of the alkyl bromide, b, based on Volhard's determination of bromide ion, and the time-interval $t_2 - t_1$. The formula is given in Part XLII.

Note Added, August 9th, 1955.—Le Roux and Swart (*J.*, 1955, 1475) have given results for the exchange of *iso*propyl bromide and of *tert.*-butyl bromide with bromide ions in acetone. Their rates, activation energies for the second-order processes, and qualitative conclusions are in essential accordance with our results.

Grateful acknowledgment is made of the help given by the late Professor S. Sugden and by Dr. C. C. Evans, particularly in the operation of the radiochemical equipment, and of a Shirtcliffe Fellowship awarded in 1942 by the University of New Zealand, and held during 1946—1948.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLVI. Kinetics of the Interaction of Iodide Ions with Simple Alkyl Bromides in Acetone.*

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Kinetic experiments on the second-order reactions of halogen substitution by potassium, sodium, and lithium iodides with seven simple alkyl bromides in acetone are reported. Reactions with the first two salts become heterogeneous, and, in the faster initial parts of the intrinsically faster reactions, errors arise from the relatively slow establishment of equilibrium in composition between the phases, a disturbance which a reduced temperature does not cure, since it lowers the rate of the surface transfers even more than the reaction rate. Reactions with lithium iodide remain homogeneous, and the main disturbance now is the negative salt effect, which, however, is not large enough in these reactions to interfere with the determination of good initial rates. The reactions are successively more reversible along the series, methyl, primary, secondary, and tertiary alkyl. The precipitations which occur with potassium and sodium salts as reagent limit the reversals, and, although the assistance of such limitation is not necessary for the kinetic study of the forward reaction in general, it had to be employed in the reaction of *tert.*-butyl bromide, which, fortunately, is not one of the faster reactions. With precautions against the errors diagnosed, rate constants and parameters of the Arrhenius equation were determined.

The early work of Conant, Kirner, and Hussey (*J. Amer. Chem. Soc.*, 1924, **46**, 232; 1925, **47**, 476, 488) on the kinetics of Finkelstein substitutions dealt specially with the reactions of potassium, sodium, and lithium iodides with a series of alkyl chlorides in acetone.

* Part XLV, preceding paper.

With potassium and sodium iodides as reagent, the alkali-metal chlorides became precipitated, with strong suppression of the back-reaction, though the substitutions are markedly reversible in homogeneous media. With lithium iodide as reagent, the solutions remained homogeneous, and the substitutions proceeded to their natural equilibria. However, it was found that, for a given alkyl chloride at a given temperature, the rate-constant of the forward reaction was substantially independent of the nature of the cation of the metal iodide, and the conclusion was drawn that the substituting agent is the iodide ion.

This was the starting point of the work now described, chronologically the first of the studies here reported together. The reactions examined were those of potassium, sodium, and lithium iodides with a series of alkyl bromides in acetone. With potassium and sodium iodides, the alkali-metal bromides became precipitated, with marked suppression of the retrograde substitutions, whilst with lithium iodide the solutions remained homogeneous, and the reactions ran to equilibrium. We went over to alkyl bromides with the idea that bromine and iodine would probably have more nearly similar properties in Finkelstein substitutions than any other pair of chemically different halogens, and that with them we might be able, with similar ease and accuracy, to examine the kinetics of substitution in both directions, and thus to pass on to a study of the thermodynamics of the reaction, as has proved to be the case.* Our main concern being with the kinetic and thermodynamic effects of simple alkyl groups in substitution, we have concentrated upon the seven groups which compose the α- and the β-methylated branching-homologous series, Me, Et, Pr^i, Bu^t, and Et, Pr^n, Bu^n, *neo*Pe (*i.e.*, *neo*pentyl). Interested as we are in the derivation of energy quantities, we have paid particular attention to effects of temperature.

As to previous work on the kinetics of reactions of alkali-metal iodides on alkyl bromides in acetone, A. G. Evans and Hamann (*Trans. Faraday Soc.*, 1951, **47**, 30) have recorded some rate constants for the reactions of potassium iodide with methyl and *iso*propyl bromide: their values are some 50% larger than ours. We think that the large discrepancy is due to their method: they tried to measure the disappearance of dissolved potassium iodide by the fall of electrical conductance, but in conditions in which a precipitate of potassium bromide was being formed between and round the electrodes, thereby contributing, by mechanical obstruction, to the fall of electrical conductance. Skolink, Day, and Miller (*J. Amer. Chem. Soc.*, **1943**, **65**, 1858) had previously declared such a method to be unsuitable, and the trials of it which have been made in these laboratories support their opinion.

We followed the disappearance of iodide ions by chemical analysis. The errors involved in our work are discussed below. We used the sealed-tube technique, which permits more accurate timing than when samples have to be taken, and avoids the difficulty of sampling those reactions mixtures in which a precipitate is formed.

Anticipating part of the following discussion and record, we find that, except for disturbances which we think can be explained and are appreciable only in a few cases, the rate-constants for a given alkyl bromide at a given temperature are independent of the nature of the cation of the saline reagent. This confirms the similar finding of Conant and his co-workers for the corresponding reactions of alkyl chlorides. We conclude, as they did, that the effective substituting agent is the halide ion, our reaction being expressible by the scheme,

$$I^- + RBr \longrightarrow RI + Br^-$$

Turning now to errors, a special group of kinetic disturbances applies to the reactions with potassium and sodium iodides. The attraction of using these reagents is that the precipitation of potassium or sodium bromide suppresses the retrograde substitution, with the result that rate constants can be calculated in the simple way applicable to an

* Some support for this idea was subsequently found in the comparison, for lithium and methyl halides in acetone, of the equilibrium constant of the chlorine–bromine Finkelstein exchange, and of the bromine–iodine exchange: the former constant is much further from unity than is the latter. For the system, LiCl + MeBr $\rightleftharpoons$ LiBr + MeCl, the equilibrium constant $K = [LiBr][MeCl]/[LiCl][MeBr]$ is 17·5 ± 1·3 in acetone at 40° (personally communicated by Dr. P. B. D. de la Mare). For the system, LiBr + MeI $\rightleftharpoons$ LiI + MeBr, the constant $K = [LiI][MeBr]/[LiBr][MeI]$ is only 1·7 at 16°, and, being nearly independent of temperature, must be about 1·6 at 40° (following paper).

irreversible reaction of the second order. Actually, owing to the finite solubilities of the metal bromides, especially of the more soluble of them, sodium bromide, the retrograde substitutions are not completely suppressed; but still, in our conditions, the reactions with potassium iodide could be carried forward to over 90% of the stoicheiometric maximum, and most of the reactions with sodium iodide could be carried to more than 75%; and thus it was easily possible to apply the equation for an irreversible reaction of the second order to the first 30—50% of reaction, thereby obtaining good rate constants appropriate to the initial conditions. The reaction of *tert.*-butyl bromide formed a partial exception. Here, the natural reversibility of the substitution is so strong that, although the reaction with potassium iodide went sufficiently far forward to allow the above procedure, the reaction with sodium iodide did not go beyond about 40% of the stoicheiometric maximum, and we could find no satisfactory way, in this case, of calculating rate constants for the forward reaction with proper allowance for such a strong, yet partly restricted, retrograde reaction.

The main kinetic disturbances to be expected from the precipitation are those due to temporary supersaturation with respect to the alkali-metal bromide, and to initial co-precipitation of some of the alkali-metal iodide with the consequent possibility of a surface reaction of the alkyl bromide. It is probable that both effects have been observed, the first leading to occasional low readings of reaction progress in the earlier part of reaction, and the second to a more regular disturbance applying mainly to the more rapid early parts of the faster reactions. Both effects were most noticeable with the most reactive alkyl bromides; and it can be understood that in rapid reactions there may not be time for the continuous maintenance of equilibrium between the phases. If we compare, for the different alkyl bromides, the initial rate constants of the heterogeneous reactions of potassium and sodium iodides with the rate constants of the completely homogeneous reactions with lithium iodide, we find that the sets of values converge to coincidence as the reactivity of the alkyl halide diminishes. For methyl bromide, the most reactive, the heterogeneous rates are on the average 19% higher than the homogeneous, for ethyl bromide they are 14% higher, and for *n*-propyl bromide 6% higher; while for the remaining, still more slowly reacting, alkyl bromides, the deviations, averaging $\pm 2\%$, are not larger than the casual kinetic error. Another regularity, applying to the reactions of methyl, ethyl, and *n*-propyl bromide, is that, for the same alkyl halide, the proportional difference between the heterogeneous and the homogeneous rates is larger at the lower temperatures. In order to account for this, we must assume that, whilst a reduced temperature retards the reaction, it retards still more the establishment of equilibrium in composition between the phases.

In the homogeneous reactions of lithium iodide with the alkyl bromides, the retrograde reactions are unimpeded. All the equilibria lie on the side of the factors, only slightly so in the methyl halide reaction, but successively more strongly so for the group of primary alkyl halides, for the *iso*propyl halide system, and for the *tert.*-butyl system. But still, by using a two-fold excess of the alkyl bromide, it was possible, for all reactions except those of the *tert.*-butyl group, to convert a sufficient proportion of the lithium iodide to enable the rates of the forward reactions to be measured. The proportions of salt converted were about 45% in the methyl case, about 30—35% in the various primary alkyl systems, and about 20% in the *iso*propyl example. In these rate measurements, we make use of the determined equilibrium compositions, and calculate with the aid of the equation for a reversible reaction of the second order in both directions.

The main rate disturbance noticed in these experiments arose from the negative salt effect characteristic of Finkelstein substitutions, in particular from its specific nature (already illustrated in Part XLIV), lithium iodide having a stronger retarding action than its equivalent of lithium bromide. (No doubt, this effect is present in the heterogeneous reactions also, though it is there masked by the disturbance due to the heterogeneity.) In the homogeneous reactions of lithium iodide with the alkyl bromides, the observation is that the second-order rate constants rise with progress of the reaction. At first the increase is so slow as to be almost lost amid the casual errors, with the result that rate-constants averaged over a considerable initial proportion of the followed reaction are indistinguishable from rate constants extrapolated to the initial conditions; but near

equilibrium the rate constants rise very appreciably. Qualitatively, this is to be expected, since lithium iodide is the more active salt, and the kinetic effect of any salt should vary more steeply with its concentration at lower than at higher concentrations. We should have liked to be able to quote the limiting rate of each forward reaction both initially and at equilibrium. But owing to the increasing drift in the rate constants near equilibrium, we could not safely make the extrapolation necessary to give rates in the neighbourhood of equilibrium compositions. We therefore cite only initial rates, which can be evaluated easily, and with the normal degree of accuracy.

The observed second-order rate constants, k_2, are given in Table 1. All these rate

TABLE 1. *Second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) for the reactions of potassium, sodium, and lithium iodides with alkyl bromides in acetone.*

[Initial concn. *a* of alkyl bromide about 0·04M throughout.]

	KI		NaI		LiI		
Temp. (c)	*b*	10^5k_2	*b*	10^5k_2	*b*	*K*	10^5k_2
			Methyl bromide				
10·0°	0·0235	6850	0·0232	6910	0·0246	0·461	6150
4·9	0·0233	4250	0·0236	4200	0·0245	0·446	3640
0·0	0·0240	2660	0·0238	2650	0·0250	0·459	2190
− 7·4	0·0241	1110	0·0238	1080	0·0231	0·433	895
−11·0	0·0238	740	0·0240	727	0·0232	0·391	582
			Ethyl bromide				
50·3	—	—	—	—	0·0229	0·159	2070
40·3	—	—	—	—	0·0232	0·138	794
40·0	0·0223	892	0·0220	889	—	—	—
35·0	0·0224	548	0·0223	544	—	—	—
32·2	—	—	—	—	0·0234	0·127	352
30·0	0·0223	330	0·0222	327	—	—	—
25·0	0·0224	197	0·0230	195	0·0237	0·119	166
20·0	0·0228	120	0·0232	117	—	—	—
17·4	—	—	—	—	0·0239	0·107	71·4
			n-*Propyl bromide*				
45·0	0·0221	1120	0·0219	1160	0·0226	0·179	1080
40·0	0·0222	731	0·0220	741	0·0197	0·156	696
35·0	0·0223	450	0·0223	424	0·0221	0·157	409
30·0	0·0223	259	0·0223	248	0·0206	0·152	238
25·0	0·0222	149	0·0230	145	0·0125	0·139	137
			iso*Propyl bromide*				
60·0	0·0217	51·0	0·0215	49·4	0·0243	0·056	48·8
55·0	0·0218	31·3	0·0216	30·6	0·0240	0·053	30·6
50·0	0·0219	19·3	0·0216	19·2	0·0242	0·050	18·7
45·0	0·0220	11·8	0·0218	11·4	0·0239	0·048	11·2
40·0	0·0223	6·97	0·0216	6·68	0·0251	0·044	6·70
			iso*Butyl bromide*				
60·0	0·0219	213	0·0216	218	0·0228	0·221	216
55·0	0·0221	134	0·0218	137	0·0229	0·193	136
50·0	0·0221	83·5	0·0218	86·4	0·0228	0·187	83·4
45·0	0·0223	52·1	0·0220	52·3	0·0239	0·173	50·8
40·0	0·0222	31·9	0·0223	31·9	0·0241	0·169	30·6
			tert.-*Butyl bromide*				
61·1	0·0214	5·63	—	—	—	—	—
52·5	0·0216	2·26	—	—	—	—	—
45·0	0·0219	1·06	—	—	—	—	—
35·4	0·0222	0·36	—	—	—	—	—
			neo*Pentyl bromide*				
98·0	—	—	—	—	0·0193	0·287	11·4
89·6	—	—	—	—	0·0195	0·287	5·31
80·6	0·0207	2·18	0·0206	2·26	0·0200	0·275	2·29
72·8	0·0209	1·01	0·0208	1·00	0·0219	0·267	1·05
64·7	0·0192	0·44	0·0194	0·45	0·0204	0·256	0·445

constants, whether calculated with the equation of an irreversible reaction, as they are for the reactions with potassium and sodium iodides, or with that of a reversible reaction, as they are for the reactions with lithium iodide, are computed from the earlier parts of the measured reactions, and thus correspond to the initial salt composition and concentration. For the reactions with lithium iodide, equilibrium constants K are given as an expression of the final compositions attained. The formula used for the reactions wth potassium and sodium iodides is

$$k_2 = [1/t(a - b)] \ln [b(a - x)/a(b - x)]$$

and the formulæ employed for the reactions with lithium iodide are

$$x = [ab/(1 - K^{-1})]\{\alpha + \beta \coth [\beta(1 - K^{-1})k_2 t]\}^{-1}$$
$$\alpha = (a + b)/2(1 - K^{-1}); \quad \beta = [1/2(1 - K^{-1})][(a - b)^2 + 4ab/K]^{1/2}$$
$$K = x_\infty^2/(a - x_\infty)(b - x_\infty)$$

where x is the concentration converted at time t, and $a = [\mathrm{RBr}]_0$, and $b = [\mathrm{KI}]_0$ or $[\mathrm{NaI}]_0$ or $[\mathrm{LiI}]_0$. The rate constants are corrected for thermal expansion of the solvent.

These data give good Arrhenius plots, for which the Arrhenius activation energies and frequency factors have been derived, which are contained in Table 2. The temperature range of the reactions of potassium and sodium iodides with *neo*pentyl bromide was inevitably somewhat small, being limited on the one side by the slowness of the reactions, and on the other by the reduced solubilities of potassium and sodium iodides in acetone at higher temperatures.

Generally, we place most reliance on the values obtained for the homogeneous reactions, though for nearly all the halides the difference between the homogeneous and the heterogeneous values are scarcely appreciable. Table 3 summarises our adopted values of the Arrhenius parameters, and contains also the absolute and relative rates at 25° for comparison with such values for other Finkelstein reactions, as given in the accompanying papers.

TABLE 2. *Parameters of the equation* $k_2 = B_2 \exp(-E_A/RT)$ *(with* B_2 *in sec.*$^{-1}$ *mole*$^{-1}$ *l. and* E_A *in kcal. mole*$^{-1}$*) for the reactions of potassium, sodium, and lithium iodides with alkyl bromides in acetone.*

	KI		NaI		LiI	
Bromide	E_A	$\log_{10} B_2$	E_A	$\log_{10} B_2$	E_A	$\log_{10} B_2$
Methyl	15·1	10·5	15·9	11·1	16·3	11·4
Ethyl	19·0	11·2	19·0	11·2	18·8	11·0
n-Propyl	19·5	11·5	19·6	11·6	19·0	11·1
*iso*Propyl	20·5	10·2	20·5	10·15	20·5	10·15
*iso*Butyl	19·8	10·3	19·9	10·2	19·9	10·3
tert.-Butyl	22·0	10·2	—	—	—	—
*neo*Pentyl	24·1	10·3	24·1	10·3	24·0	10·2

TABLE 3. *Rate constants (*k_2 *in sec.*$^{-1}$ *mole*$^{-1}$ *l.), relative rates at common temperatures, and adopted values of the Arrhenius parameters (*B_2 *in sec.*$^{-1}$ *mole*$^{-1}$ *l. and* E_A *in kcal. mole*$^{-1}$*), for the reactions of iodide ions with alkyl bromides in acetone (salt, 0·022*M*-iodide).*

Bromide	Me	Et	Pr^i	Bu^i	Pr^n	Bu^i	*neo*Pe
$10^5 k_2$ (25°) ...	25,000	166	1·3	0·10 *	137	6·0	0·0020
Rel. k_2 (25°) ...	145	1	0·0078	0·00051 *	0·82	0·036	0·000012
$\log_{10} B_2$	11·4	11·0	10·2	10·2 *	10·8	10·3	10·2
E_A	16·3	18·8	20·5	22·0 *	18·7	19·9	24·0

* Values when using potassium iodide.

EXPERIMENTAL

The alkyl bromides were prepared or purified as described in Part XLIII, and acetone was purified as noted in Part XLII. Potassium and sodium iodides were crystallised from water, and lithium iodide from acetone; and all these iodides were dried in a vacuum at 110° over phosphoric oxide.

Kinetics.—(a) *Methods.* Each sealed tube contained 10 c.c. of solution and enclosed an air-space of 5 c.c. Each was charged, first with 5 c.c. of a solution in dry acetone of the metal iodide, and after this had been cooled to −80°, with 5 c.c. of a solution of the alkyl bromide, jacketed automatic pipettes being used. The solutions were made up by weighing, excepting that of methyl bromide, which was made up in an approximate way first, and was then standardised by quantitative hydrolysis with potassium hydroxide. The reaction mixtures involving *neo*pentyl bromide were prepared with omission of the precaution, unnecessary in this case, of cooling to −80°.

For the reactions which were to be calculated with the formula from irreversible reactions of the second order, the tubes were shaken for 30 sec. after immersion in the thermostat. The end of this period was taken as the time-zero, and the analytical result obtained from a tube withdrawn at that moment was used in order to deduce the initial concentrations a and b of the reactants, as well as the concentration x_0 converted during warming, a quantity by which all the conversions x, as measured at later times, had to be corrected.

For reactions which were to be calculated with the formulæ of reversible reactions of the second order, a different principle was employed in order to establish kinetically initial conditions. Identical tubes, originally at a temperature so low that no reaction proceeded, were placed in the thermostat at a time t_a. Suppose that their contents are sensibly at thermostat temperature at a time t_c. At two successively later times t_1 and t_2, so chosen that the reaction–time curve can be treated as linear from t_c to t_2, tubes were withdrawn and analysed, the concentrations converted being x_1 and x_2, respectively. There exists a time t_b, between t_a and t_c, such that, if the tubes had, at t_b, been raised instantaneously to thermostat temperature, then, at all times after t_c, the amount of conversion would have been what it is actually found to be. This time t_b is the kinetic time-zero, and it is found by extrapolating the straight line through the points (x_1, t_1) and (x_2, t_2) back to the axis $x = 0$. At this time-zero, the initial concentrations a and b of the reactants are to be taken as the concentrations originally introduced, and the concentration converted is to be taken as zero.

The analyses were made by Lang's iodine cyanide method. A withdrawn tube was chilled to −80°, and broken under 30—40 c.c. of an aqueous solution 2N in sulphuric acid and 0·5N in hydrochloric acid. After the addition of 5 c.c. of 15% potassium cyanide solution, the mixture was titrated with 0·005N-potassium iodate, starch being the indicator.

(b) *Results.* These are summarised in Table 1. An example of a kinetic run is given in Table 4.

TABLE 4. *Rate of reaction of alkali-metal iodides with alkyl bromides in acetone: example* LiI + MeBr ⟶ LiBr + MeI.

(Temp. −7·39°. Initially, [MeBr] = 0·04350M; [LiI] = 0·02311M.)

t (sec.)	x (M)	10^3k_2 (sec.$^{-1}$ mole^{-1} l.)	t (sec.)	x (M)	10^3k_2 (sec.$^{-1}$ mole^{-1} l.)
88	0·00080	—	1018	0·00669	8·92
358	0·00289	8·94	1198	0·00742	8·88
508	0·00391	8·92	1558	0·00874	8·98
658	0·00479	8·84	2098	0·01009	9·12
838	0·00580	8·90	∞	0·01232	—

(In this Table, t and x are corrected throughout as explained in the preceding section.)

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLVII. Kinetics of the Interaction of Bromide Ions with Simple Alkyl Iodides in Acetone.*

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Kinetic experiments on the second-order reactions of halogen substitution by lithium bromide with five simple alkyl iodides in acetone are reported. The reaction of methyl iodide is moderately reversible, but those of the other alkyl iodides comparatively slightly so. In accordance with the general rules governing salt effects in Finkelstein substitutions, the salt effect in this substitution so operates tha tthe rate constants fall at first with reaction progress, but attain relatively steady values near equilibrium. Here the salt present is mainly lithium iodide, and it is for such salt conditions that the determined rate constants have been evaluated. From them, parameters of the Arrhenius equation are derived for the reactions of the five alkyl groups directly studied; and approximate parameters have been deduced by an indirect method for a sixth alkyl group.

The particular Finkelstein reaction, the kinetics of which are here to be described, is that between an ionic bromide as substituting agent and a series of simple alkyl iodides in anhydrous acetone as solvent. We know of no previous kinetic investigation of this substitution.

The reaction is the reverse of that, considered in the preceding paper, between potassium, sodium, or lithium iodide and alkyl bromides; but in the present work we were restricted to the use of lithium bromide as reagent, since potassium and sodium bromides are insufficiently soluble in dry acetone to be thus employed. However, because of the principle of microscopic reversibility, consistency with the conclusion, reached in the preceding paper on the basis of a comparison of the kinetics of the reactions of the three alkali-metal iodides on alkyl bromides, requires the assumption that, in the reaction between lithium bromide and alkyl iodides, the bromide ion is the essential substituting agent:

$$Br^- + RI \longrightarrow RBr + I^-$$

We have examined this reaction for the following five alkyl groups: Me, Et, Pr^n, Pr^i, and Bu^i. In each case, rates have been measured over a temperature range, and the parameters of the Arrhenius equation have been computed. An attempt to complete our examination of the α-methylated branching homologous series by including the *tert.*-butyl group was frustrated by the instability of *tert.*-butyl iodide in the solvent at the temperatures required for the substitution. Although we did not directly complete the study of the β-methylated series by investigating the kinetics of the reaction of lithium bromide with *neo*pentyl iodide, we are able to complete it indirectly to the extent of deriving an approximate Arrhenius equation for the rate of this reaction by combining the kinetic data given in the preceding paper for the reaction between lithium iodide and *neo*pentyl bromide with the thermodynamic constants of the balanced bromine–iodine exchange reaction of the *neo*pentyl group.

The reactions between lithium bromide and the five alkyl iodides for which we report rate constants all ran to equilibria which were well towards the right-hand side of the above chemical equation. With the alkyl iodides initially present in two-fold excess, the conversion of salt by methyl iodide went forward to the extent of about 75%, its conversion by ethyl, *n*-propyl, and *iso*butyl iodide to the extent of approximately 90%, and by *iso*propyl iodide to more than 95%, of the stoicheiometric maximum. Had it not been for the kinetic disturbance next to be mentioned, it should have been possible to calculate rate constants for considerable portions of all these reactions by the formula for an

* Part XLVI, preceding paper.

irreversible reaction of the second order. In fact, however, we always used the equations for a reversible reaction in computing rate constants for these reactions.

The reason for this was that the salt effect, particularly its specific nature with respect to the individual salts, so operates in this reaction as to produce a drift in the rate constants, which is somewhat sharp near the commencement of reaction, but relatively slight near equilibrium. As a result, we found it unsatisfactory in most cases to attempt the extrapolations necessary for the determination of initial rate constants, and were able to assign reasonably good limiting rate constants only at the other limit, that is, for salt compositions in the neighbourhood of those at equilibrium. Having therefore decided on the extraction only of final rate constants from the kinetic measurements, the rate constants had to be calculated with the equation for a reversible reaction of the second order.

The salt effect described is consistent with the observations on salt effects noted in the preceding papers, and with some direct investigations on salt effects which are to be reported later. The qualitative rules appear to be as follows. All alkali-metal salts of strong acids depress the rate of Finkelstein substitutions in acetone. Lithium iodide has a considerably greater specific retarding effect than lithium bromide; and indeed the order of intensity of the salt effect among the four lithium halides is probably LiI > LiBr > LiCl > LiF, though the only evidence that we could offer at present for the inclusion of lithium fluoride in this series applies, not to solvent acetone, but to nitromethane as solvent. For any one salt, the kinetic effect of a given increment of concentration is very much greater at low than at high concentration. From these rules it follows that, in a reaction between lithium bromide and an alkyl iodide, the reaction rate will fall as the original salt becomes progressively replaced by the kinetically more effective lithium iodide; and also that the fall will be sharp at first, when the more effective salt is in very low concentration, but relatively slight later, when this salt has attained a considerable concentration. Similarly, we can understand how, in the reaction, described in the preceding paper, between lithium iodide and an alkyl bromide, the rate constants rise, as the original salt becomes gradually replaced by the kinetically less effective lithium bromide, but rise scarcely perceptibly at first, and then more markedly, although still not steeply, near equilibrium. Near the beginning of this reaction, the salt effect is due almost entirely to the lithium iodide in relatively high concentrations, and, near the end, most of the salt effect will still be due to lithium iodide, which remains in considerable concentration as it is the preponderating salt at equilibrium.

TABLE 1. *Second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of the reaction between lithium bromide and* iso*propyl iodide in acetone at* 69·84°.

(Initially, [Pr^{i}I] = 0·04010M = a, [LiBr] = 0·02183M = b, x = 0, and t = 0, this time-zero being 6 sec. later than the moment of insertion of the reaction tubes, with shaking, into the thermostat. From the value of x noted below, the following are calculated: K = 25·4; α = 0·0322M; β = 0·0113M.)

t (corr.) (sec.)	x (mole l.$^{-1}$)	Salt converted (%)	10^3k_2	t (corr.) (sec.)	x (mole l.$^{-1}$)	Salt converted (%)	10^3k_2
150	0·00367	16·8	3·22	870	0·01150	51·6	2·53
240	0·00522	23·9	3·05	1170	0·01350	61·8	2·45
340	0·00656	30·1	2·88	1560	0·01471	67·5	2·38
460	0·00805	36·9	2·81	2100	0·01642	75·3	2·32
630	0·00967	44·3	2·70	∞	0·02093	95·9	—

(The value of k_2 extrapolated to equilibrium is 2·23 × 10^{-3} sec.$^{-1}$ mole^{-1} l.)

In illustration of the foregoing description of the marked effect of the changing composition of lithium salts on the kinetics of the reaction between lithium bromide and alkyl iodides, the details of a run with *iso*propyl iodide are recorded in Table 1. Here a and b are the initial concentrations $[RI]_0$ and $[LiBr]_0$, respectively, and x is the concentration converted at time t, the times being corrected to correspond to a time-zero determined by the method described in the preceding paper as appropriate for reversible reactions. From the final value x_∞ of x, an equilibrium constant is calculated:

$$K = x_\infty^2/(a - x_\infty)(b - x_\infty)$$

and from this the concentrations α and β, defined below, are derived :

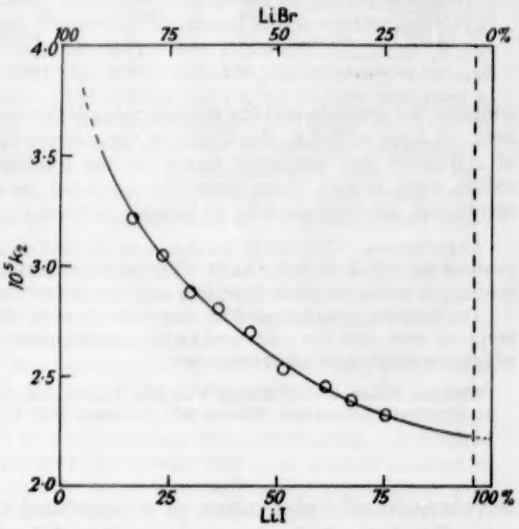
$$\alpha = (a + b)/2(1 - K^{-1}); \quad \beta = [1/2(1 - K)^{-1}][(a - b)^2 + 4ab/K]^{1/2}$$

The second-order rate constants k_2 are now computed from the equation

$$x = [ab/(1 - K^{-1})]\{\alpha + \beta \coth [\beta(1 - K^{-1})k_2 t]\}^{-1}$$

All concentrations are corrected for thermal expansion of the solvent.

The nature of the extrapolations involved in the deduction of limiting rate constants is illustrated in the Figure, which refers to the same kinetic run. The plot is of the calcul-



Effect of changing composition of lithium halides of total concentration 0·0218M *on the second-order rate constant of the reaction of lithium bromide with* isopropyl *iodide in acetone at* 69·8°.

The vertical broken line represents equilibrium concentration.

ated second-order rate constant against the percentage of salt converted. On its left, the curve is expected to take a sharper turn upwards near the axis of ordinates, where the concentrations of the kinetically more effective salt vanish; and for this reason the extrapolation required to give an initial rate for reaction is considered impracticable. On its right, the curve should become more nearly horizontal as it approaches the salt-composition corresponding to equilibrium; and it is by extrapolation in this direction that the cited value of the final rate constant is obtained.

The complete series of final second-order rate constants, derived in this way, is given

TABLE 2. *Final second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) for the reactions of lithium bromide with alkyl iodides in acetone.*

[Initial concn. *a* of alkyl bromide about 0·04M throughout.]

RI	Temp. (° c.)	*b*	*K*	$10^5 k_2$	RI	Temp. (° c.)	*b*	*K*	$10^5 k_2$
MeI	16·5	0·0235	1·74	21,900	Pr^{i}I	69·8	0·0218	25·4	2230
	8·0	0·0238	1·81	9600		60·3	0·0221	27·9	1030
	0·0	0·0241	1·86	3940		50·3	0·0224	31·6	438
	−11·0	0·0205	1·87	1160		39·9	0·0227	35·5	171
EtI	39·9	0·0227	7·58	5980	Bu^{i}I	75·0	0·0217	4·44	2720
	32·2	0·0230	7·87	3020		59·8	0·0225	4·83	962
	25·0	0·0232	8·70	1490		49·0	0·0229	5·18	380
	16·5	0·0235	9·01	615		37·2	0·0229	5·71	119
Pr^{n}I	37·2	0·0252	6·17	3440					
	26·3	0·0252	6·90	1180					
	8·4	0·0259	8·62	170					
	−5·8	0·0264	11·24	30·7					

in Table 2. They refer throughout to salt conditions which, though not strictly standardised, involved salt consisting predominantly of lithium iodide, the total salt concentration being always close to 0·023M.

These rate constants give satisfactory Arrhenius plots, from which the energies of activation and frequency factors shown in Table 3 have been derived. The same Table

TABLE 3. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), and relative rates at 25°, and parameters of the equation $k_2 = B_2 \exp(-E_A/RT)$ (with B_2 in sec.$^{-1}$ mole^{-1} l., and E_A in kcal. mole^{-1}) for the reactions of lithium bromide with alkyl iodides in acetone (salt 0·023M, mainly lithium iodide).*

R in RI *	Me	Et	Pr^i	Pr^n	Bu^n	*neo*Pe
$10^5 k_2$ (25°)	27,000	1490	37	1050	32	—
Rel. k_2 (25°)	18	1	0·025	0·71	0·021	—
$\log_{10} B_2$	11·4	11·1	10·2	10·8	10·3	10·1
E_A	16·3	17·7	18·5	17·5	18·8	23·1

contains the absolute and the relative rates of the reactions at 25°. For greater completeness, we have added to the Table, in the column headed "*neo*Pe" the Arrhenius energy of activation and frequency factor for the reaction of lithium bromide with *neo*pentyl iodide, even though these quantities have not been directly measured, but, as already mentioned, were obtained by an indirect method.

Experimental.—The alkyl iodides were purified as indicated in Part XLIV. Acetone was purified as noted in Part XLII. Lithium bromide was crystallised from the concentrated solution in water, and was dried in a vacuum at 110° over phosphoric oxide.

The kinetics were followed by the sealed-tube method, with the procedure for starting and stopping runs, and the analytical technique, described in the preceding paper for the reactions of lithium iodide with alkyl bromides.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLVIII. Kinetics of the Interaction of Iodide Ions with Simple Alkyl Iodides in Acetone.*

By P. B. D. DE LA MARE.

[Reprint Order No. 6212.]

Kinetic experiments on the second-order reactions of iodine exchange between lithium iodide and four simple alkyl iodides in acetone are reported. In the one case of *tert.*-butyl iodide the bimolecular substitution is accompanied by a probably unimolecular side-reaction, in an amount which is kinetically appreciable, but not too large to permit evaluation and correction. Salt conditions are standardised, and rate constants and parameters of the Arrhenius equation are determined.

NEARLY all previous investigations of the rate of iodine exchange between alkali-metal iodides and alkyl iodides relate to the reaction in solvent methyl or ethyl alcohol, which, owing to its tendency to enter into solvolytic reactions, is unsuitable as a medium for the halogen exchanges of tertiary and certain other alkyl halides. This type of medium was used by Seelig and Hull for the exchanges of *n*- and *iso*-propyl iodide (*J. Amer. Chem. Soc.*, 1942, **64**, 940), by McKay for those of a number of primary, secondary, and tertiary alkyl iodides (*ibid.*, 1943, **65**, 702), by Neimen and Protsenko for ethyl iodide (*Doklady Akad. Nauk S.S.S.R.*, 1950, **71**, 327), by May, Daudel, Schotsky, Sarraf, and Vobauré for ethyl and allyl iodide (*Compt. rend.*, 1951, **232**, 727; 1952, **235**, 935; *J. Chim. phys.*, 1952, **49**, 64),

* Part XLVII, preceding paper.

by Van Stratten, Nickolls, and Winkler for 1-methylhexyl and several *cyclo*alkyl iodides (*Canad. J. Chem.*, 1951, **29**, 372), and by Kuhn, Stilman, Purlee, and Reibsomer for benzyl iodides (*J. Amer. Chem. Soc.*, 1953, **75**, 3579; 1954, **76**, 1796). McKay's work was designed as a study of the effect of alkyl structure: it included some examination of the temperature coefficients of reaction rate, but not with sufficient extension to enable individual Arrhenius parameters to be quoted, though it is mentioned that the primary alkyl iodides gave energies of activation near 19, and the secondary values near 20·5 kcal./mole.

As to the kinetics of the exchange in non-hydroxylic solvents, Hughes, Juliusberger, Masterman, Topley, and Weiss examined the reaction between 1-methylheptyl iodide and sodium radio-iodide in solvent acetone (*J.*, 1935, 1525) and May, Daudel, Schotsky, Sarraf, and Vobauré studied analogous reactions of ethyl and allyl iodide in solvent acetonitrile (*locc. cit.*). However, no systematic work concerning structural effects on the kinetics of this exchange reaction in non-hydroxylic solvents has yet been reported.

As in the work described in the accompanying papers, so in the present study of halogen exchange between sodium radio-iodide and alkyl iodides, anhydrous acetone was used as solvent. The series of alkyl iodides employed was less complete than in the investigation of some other Finkelstein substitutions, but it was sufficient to show the main trends. Methyl iodide excluded itself by the rapidity of its reaction, but rate data have been obtained for the other members of the α-methylated branched-homologous series, ethyl, *iso*propyl, and *tert.*-butyl iodide, and also for the end members of the β-methylated series, ethyl and *neo*pentyl iodide.

The reactions were conducted in ampoules, one for each measurement of the extent of exchange. Each measurement involved separating the sodium iodide from the organic iodide, and noting the loss of radioactivity from the former. The separations were effected either by evaporation, or by partition between ether and water.

The exchange with *tert.*-butyl iodide was accompanied by a side reaction, which could be minimised, but not wholly eliminated, by conducting all manipulations under nitrogen and in dim light, and by using blackened ampoules for the kinetic runs. The main part of this residual side reaction is believed to be a unimolecular olefin elimination. It resulted in the appearance in the solution of hydrogen iodide was well as of a small amount of iodine. These substances must very quickly come into radioactive equilibrium with the sodium iodide; but in the separation, as conducted by evaporation, of the *tert.*-butyl iodide from the sodium iodide, hydrogen iodide and iodine are removed with the *tert.*-butyl iodide, which therefore becomes credited with too large an uptake of radioactivity from the sodium iodide. A correction for this additional exchange, resulting from the side reaction, was made as follows: A series of blank determinations was carried out, in each of which an ampoule, charged only with a solution of *tert.*-butyl iodide in acetone, was left at the temperature, and for approximately the length of time, of a determination of the exchange resulting from the reaction with sodium iodide. To the product of such a blank run, sodium radio-iodide was added; and then it was immediately separated by the evaporation method, and its radioactivity was measured. The loss of radioactivity was that due to the side reaction only, and the rate of such loss represented the negative correction to be applied to the total rate of loss as measured in the main exchange experiments. In the conditions employed, the side reaction was found to be responsible for some 10—15% of the total observed exchange.

Like other Finkelstein substitutions, the iodine exchange reaction shows a negative salt effect, which is the subject of a separate investigation later to be published by Dr. R. W. Broadbank. His results have been used in order to make the small corrections necessary for the purpose of reducing the present rate constants to a comparable basis at the common salt concentration 0·1M.

The kinetic results are in Table 1, except that here the rate constants for the exchange reaction of *tert.*-butyl iodide remain uncorrected for the side reaction. The data permitting this correction, and the corrected rate constants for the exchange of *tert.*-butyl iodide, are given in Table 2. In Table 1, C, $C - X_1$, $C - X_2$, are counting rates applying to the main series of exchange runs. They represent respectively the specific activity of the sodium iodide initially, on separation at a time t_1, soon after the reaction solution had

TABLE 1. *Second-order rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of iodine exchange between alkyl iodides and sodium radio-iodide in acetone.*

Ethyl iodide

Temp. (c)	a = [AlkI]	b = [LiBr]	$t_2 - t_1$ (min.)	Counting rates C	$C - X_1$	$C - X_2$	10^5k_2 (b)	10^5k_2 (0·1)	Mean
− 5·7°	0·3408	0·1004	18·2	367·0	321·0	159·9	225 ± 6	225	—
,,	0·3453	,,	25·2	,,	,,	136·1	211 ± 5	211	—
,,	0·3396	,,	20·2	,,	,,	154·2	218 ± 7	218	218
−17·3	0·3495	0·1022	34·0	439·0	398·2	290·1	48·8 ± 2·3	48·9	—
,,	0·3514	,,	56·0	,,	,,	239·5	49·6 ± 1·5	49·7	—
,,	0·3551	,,	76·0	,,	,,	207·8	48·3 ± 1·3	48·3	49·0
−27·3	0·3650	0·1035	107·0	439·0	424·7	324·3	12·2 ± 0·8	12·2	—
,,	0·3632	,,	121·0	,,	,,	313·2	12·3 ± 0·7	12·4	12·3

*iso*Propyl iodide

10^5k_2 (b)	10^5k_2 (0·1)
a 0·1199, b 0·0839; 25·0°	
62·8 ± 1·4	61·8
56·9 ± 1·3	56·0
57·4 ± 1·3	56·5
61·3 ± 1·4	60·3
59·9 ± 1·4	58·9
Mean	58·7
a 0·1243, b 0·0869; −0·1°	
2·83 ± 0·08	2·79
3·26 ± 0·09	3·21
2·92 ± 0·08	2·88
2·94 ± 0·08	2·91
2·90 ± 0·08	2·86
Mean	2·93

tert.-Butyl iodide *

10^5k_2 (b)	10^5k_2 (0·1)
a 0·1118, b 0·0944; 44·6°	
165 ± 7	164
181 ± 8	180
193 ± 8	192
198 ± 9	197
167 ± 7	166
Mean	180
a 0·1151, b 0·0972; 25·0°	
21·6 ± 0·6	21·6
22·9 ± 0·6	22·8
21·8 ± 0·6	21·7
21·7 ± 0·6	21·7
20·5 ± 0·6	20·5
Mean	21·7
a 0·2085, b 0·0838; 25·0°	
20·8 ± 0·7	20·3
20·1 ± 0·7	19·6
21·4 ± 0·7	19·9
19·6 ± 0·7	19·1
21·5 ± 0·7	21·0
Mean	20·2
a 0·5142, b 0·0572; 25·0°	
22·0 ± 1·0	21·3
22·8 ± 1·0	22·1
21·4 ± 0·9	20·7
Mean	21·4
a 0·5142, b 0·1434; 25·0°	
17·3 ± 0·5	17·9
16·5 ± 0·5	17·1
Mean	17·5
a 0·2160, b 0·0868; −0·1°	
0·684 ± 0·026	0·677
0·747 ± 0·028	0·740
0·744 ± 0·028	0·737
0·704 ± 0·027	0·697
0·690 ± 0·026	0·683
Mean	0·707

neo*Pentyl iodide*

10^5k_2 (b)	10^5k_2 (0·1)
a 0·1705, b 0·0781; 64·7°	
9·48 ± 0·20	9·20
9·10 ± 0·16	8·84
9·31 ± 0·15	9·04
9·46 ± 0·14	9·18
Mean	9·06
a 0·1760, b 0·0806; 44·6°	
1·19 ± 0·03	1·17
1·16 ± 0·03	1·13
1·11 ± 0·03	1·08
1·16 ± 0·02	1·13
Mean	1·13
a 0·1786, b 0·0818; 35·0°	
0·484 ± 0·011	0·474
0·446 ± 0·010	0·437
0·442 ± 0·010	0·433
Mean	0·448

* Rates uncorr.; see Table 2.

TABLE 2. *Rate corrections calculated as coefficients (k_2' in sec.$^{-1}$ mole^{-1} l.) of the side reaction of* tert.*-butyl iodide in acetone, and corrected rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.) of iodine exchange between* tert.*-butyl iodide and sodium radio-iodide in acetone.*

Temp. (c)	a = [ButI]	t' (min.)	Counting rates C	$C - X'$	$10^5k_2'$	10^5k_2 (0·1) Uncorr.	Corr.
44·6°	0·112	34	618·2	588·6	22	180	158
25·0	0·115	240	682·2	647·9	3·2	21·7	18·5
,,	0·208	234	711·0	666·4	2·1	20·2	18·1
,,	0·514	195	533·4	492·3	2·0	21·4	19·4
,,	0·514	195	553·4	529·0	0·7	17·5	16·8
−0·1	0·216	7470	488·0	453·5	0·077	0·707	0·630

attained the temperature of the thermostat, and on separation at some later time t_2. In Table 2, C and $C - X'$ are counting rates applying to the blank runs, which were made with *tert.*-butyl iodide for the purpose of measuring the side-reaction. They represent respectively the specific activity of the sodium iodide when untreated, and when recovered after having been mixed with a solution of *tert.*-butyl iodide which had previously been kept for a period t' at the experimental temperature. The ± errors attached to the rate-constants entered in Table 1 are errors deriving from the probable errors of radioactive counting, which are calculable from the size of the counts.

Because of the side-reaction, the measurements on *tert.*-butyl iodide are less satisfactory than those on the other alkyl iodides. Although the side-reaction is probably unimolecular, the main reaction of exchange, as is shown by the experiments conducted at 25° with

different concentrations of sodium iodide, must have substantially a second-order kinetic form.

Table 3 assembles the parameters of the Arrhenius equation for these exchange reactions, and the absolute and relative rates at 25°, as given by the Arrhenius equation with the parameters listed. The data will be discussed in Part XLIX.

TABLE 3. *Rate constants (k_2 in sec.$^{-1}$ mole^{-1} l.), relative rates at a common temperature and parameters (B_2 in sec.$^{-1}$ mole^{-1} l., and E_A in kcal. mole^{-1}) of the equation $k_2 = B_2 \exp(-E_A/RT)$ for the reactions of sodium radio-iodide with alkyl iodides in acetone.*

Alkyl iodide	Et	Pr^i	Bu^t	*neo*Pe
$10^5 k_2$ (25°)	6000	53	18	0·11
Rel. k_2 (25°)	1	0·0088	0·0030	0·000018
$\log_{10} B_2$	11·5	11·0	12·0	10·2
E_A	17·4	19·4	21·5	22·0

EXPERIMENTAL

The acetone and the alkyl iodides were purified or prepared as described in Part XLIV. The *neo*pentyl iodide had b. p. 67°/90 mm., n_D^{20} 1·4885, n_D^{25} 1·4860. The *tert.*-butyl iodide, after purification by fractionation under nitrogen, had b. p. 25°/60 mm., 48·5°/120 mm., was kept with mercury in small sealed tubes, and was redistilled at 10 mm. immediately before use.

The National Institute for Medical Research very kindly made available solutions containing carrier-free iodine (half-life 8 days) as iodide ions, together with a little stabilising material, usually sodium hydrogen sulphite. It was not thought necessary to remove the latter, since the amount present, after dilution of the sample with inactive iodide, was only of the order of 0·001% of the weight of sodium iodide. The solution of radioactive material was added to about 10 g. of sodium iodide dissolved in acetone, and the solution was filtered and evaporated. The residual radioactive sodium iodide was dried in a vacuum and dissolved in dry acetone.

The sealed-tube method was used for the kinetics. For the reactions of *iso*propyl, *tert.*-butyl, and *neo*pentyl iodide, solutions of the alkyl iodide and of sodium radio-iodide were delivered by automatic pipettes protected from atmospheric moisture by tubes of calcium chloride, into dried ampoules. Each ampoule was immediately sealed, and cooled to and kept at −80° until required. The additional precautions taken with *tert.*-butyl iodide have already been noted.

For these alkyl iodides, reaction was stopped by strongly cooling the ampoules withdrawn from the thermostat. The separation of the organic from the inorganic iodide was effected by evaporation below 0° with the aid of a high-capacity pump. Similar methods were used in blank determinations of the side reaction undergone by *tert.*-butyl iodide.

The exchange reaction of ethyl iodide was too rapid to admit the above technique. In this case the reaction mixtures were made by breaking a bulb containing a weighed amount of ethyl iodide within an ampoule containing the sodium radio-iodide in the acetone at −80°. After a period in the thermostat, reaction was stopped by cooling the withdrawn ampoule to −80°. The ethyl iodide was then separated from the sodium iodide by partition between water and ether. The aqueous solution of sodium iodide was evaporated to dryness, and the residue was, as usual, dissolved in water, and made up to a suitable volume for counting.

The general procedure of counting and calculation is as given in Parts XLII and XLV. In the present case, the amount of radioactive decay during a single run was appreciable, but small, and it was thus an easy matter to correct the counts to a standard time by means of the known decay constant of the single radioactive species. Second-order kinetic constants were corrected for thermal expansion of the solvent, and were adjusted to correspond to the salt concentration 0·1M as already described.

Correction for the side reaction of *tert.*-butyl iodide was effected by calculating as a second-order rate-constant the measured exchange due to the side-reaction in a time approximately equal to that of the exchange run to which the correction was to be applied, and then subtracting the constant from the second-order rate constant deduced from the exchange run, or rather, in practice, from the mean of such constants obtained from a group of similar exchange runs.

The valuable help of the National Institute of Medical Research in supplying carrier-free 131-iodide ion is gratefully acknowledged.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLIX. Analysis of Steric and Polar Effects of Alkyl Groups in Bimolecular Nucleophilic Substitution, with Special Reference to Halogen Exchanges.*

By P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie.

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In continuation of the work (1946) of Dostrovsky, Hughes, and Ingold on the subject indicated in the title, the assumptions underlying their analysis are critically examined. One major modification of method is then introduced. On this basis, their calculations of the energetic effects produced by alkyl groups on the kinetics of the bromine-exchange reaction are revised. And they are extended to substitutions involving chlorine and iodine. They are also extended by a calculation of the associated entropic effects. The results are as follows.

In these reactions, the steric energetic effects of the alkyl groups are always retarding. But, contrary to earlier ideas of steric hindrance, such effects depend only slightly, and not always in the preconceived sense, on the sizes of the halogen atoms. They depend strongly on the structures of the alkyl groups, in which successive β-substitution starts by being less important, but, again contrary to older preconceptions, ends by being much more important, than successive α-substitution. The polar energetic effects of the alkyl groups are retarding, and are associated almost exclusively with α-substitution.

Three kinds of structural entropic effects, called ponderal,† steric, and polar, are recognised, which depend on the incidence and distribution of mass, bulk, and charge, respectively. The ponderal effect, which would be exerted by massive, but non-space-filling, non-polar particles, such as neutrons added by isotopic substitution, is retarding in general, though a sufficient accumulation of new masses, near the reaction centre will weaken this effect, and could conceivably reverse it. Contrary, again, to elementary preconceptions, the steric entropic effect is accelerating if the steric thrust on the attacking reagent is directly outwards, but retarding if the main effect of it is to deflect the reagent sideways. The polar entropic effects of alkyl groups are negligible.

The quantitative analysis is made from first principles, without the use of adjustable constants, excepting one polar constant for the whole family of groups and reactions. The energies of activation and frequency factors thus calculated are compared with the available experimental values. The agreement is good generally, though only fair for reactions of the *neo*pentyl group; and a plausible reason for the lower accuracy obtained with this last group is suggested. Calculated effects of alkyl structure on the rates themselves agree with observed rates to a factor of 2·5 over that range, 10^4, of rates which excludes the *neo*pentyl group, and to a factor of 5·5 over the complete range, 10^7, of rates which includes this group. There is thus some experimental support for the genuineness of the pattern of effects described by theory. Proposed extensions of the theoretical treatment, *e.g.*, to bimolecular nucleophilic substitutions of a more general character are briefly indicated.

For some decades the theory of steric hindrance remained undeveloped, because its dependence on the details of reaction mechanism was not understood, and in any case such details were unknown. Later, when the mechanisms of some general reactions became known well enough to permit a geometrical and electronic description of their transition states, it became possible, not only to foretell from the mechanism in operation whether steric hindrance would, or would not, be present in principle (Hughes, *Trans. Faraday Soc.*,

* Part XLVIII, preceding paper. † Cf. footnote, p. 3216.

1941, **37**, 620; Day and Ingold, *ibid.*, p. 686), but also to make a beginning on the problem of quantitatively calculating expected steric effects on reaction rate.

Such calculations have been reported for bimolecular nucleophilic substitutions in a series of simple alkyl halides (Hughes, *loc. cit.*; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173), but at a time when the experimental material available for comparison with the calculated results was comparatively slight. However, the calculations have since been extended; and additional experimental results have now become available, as recorded in the accompanying papers. In this paper we report the further calculations, and with their aid discuss the new experimental material.

The previous calculations were developed in detail in the example of the bromine-exchange reaction,

$$Br^- + RBr \longrightarrow BrR + Br^-$$

for the seven alkyl groups, which compose the α- and the β-methylated series of branching homologues, Me, Et, Pr^i, Bu^t, and Et, Pr^n, Bu^i, *neo*Pe (*neo*pentyl). The object was to compute the energy of mutual compression of all atoms not directly bonded together, both in the transition state of substitution, and in the initial alkyl bromide molecule, and thus to obtain the excess of non-bonding energy involved in the formation of the transition state. This excess represented the calculated contribution of steric hindrance to the activation energy of the reaction. The simplifications employed precluded any attempt to discuss, even qualitatively, the effect of steric hindrance on the entropy of activation.

In the present extension of this work, our first proceeding will be to set out the assumptions and approximations involved in the previous calculations, and to reconsider some of the more questionable of them, particularly as to the possible influence of any such uncertainties on the results. We shall then introduce one major modification of method, and on this basis revise the former calculations. We shall also extend them, in their revised form, to the two other exchange reactions,

$$Cl^- + RCl \longrightarrow ClR + Cl^-$$
$$I^- + RI \longrightarrow IR + I^-$$

in order to have a range of theoretical results more nearly representative of the experimental data now available. And we shall further extend them to include a quantitative discussion, the first of its kind, so far as our knowledge of the literature extends, of structural effects, including those of steric hindrance, on entropy of activation, and so on the frequency factor of reaction rate. Finally, we shall summarise the observations, and discuss them in the light of the calculations.

(A) Consideration of Assumptions and Approximations.

(a) *Statement of Initial Assumptions and Approximations.*—The first set of geometrical assumptions employed by Dostrovsky, Hughes, and Ingold (*loc. cit.*) was as follows. The initial molecules were taken to have normal covalent bond-lengths, and tetrahedral bond-angles. In the transition states, the same assumption was made for all bonds except those of the α-carbon atom, whose three bonds to hydrogen or carbon were given a normal length, but were taken as trigonally disposed in a plane, to which the oppositely directed, semi-ionic semi-bonds to the two halogen atoms were perpendicular. The common length of the equivalent semi-bonds had to be specially computed, as noted below. The geometry so far specified was assumed to be determined entirely by the bonding forces. Non-bonding forces were allowed to determine rotational conformations, but not to stretch or bend bonds. The forms of the resulting transition-states of substitution of the seven alkyl groups considered are diagrammatically represented in the paper cited. It will be convenient to describe this type of model as " stiff," even though rotations are allowed, the reference being to the assumed restrictions on the stretching and bending of bonds by non-bonding forces.

For the computation, from these models, of the various non-bonding pressures, certain dynamical assumptions were necessary. Of the two types of force-law that have been

successfully employed in work on pressure–volume relations, the one involving an exponential, and the other a power-law, repulsive potential, the former was adopted. Specifically, the energy W of non-bonding interaction of any pair of atoms at a nuclear separation r was assumed to be

$$W = -Ar^{-4} - Br^{-6} + be^{-r/0.345}$$

the first term representing electrostatic attraction, the second electrokinetic attraction, and the third steric repulsion. The coefficients A and B can be computed from known atomic constants, whilst b has to be evaluated empirically, using the condition that dW/dr vanishes when r equals the van der Waals distance. The length-constant, 0·345 Å, is also empirical, and was found by Born and Mayer to be the best general value for application to a considerable number of kinds of atom-pairs. It was selected in preference to any of the values which have been theoretically derived for certain cases by relatively crude methods of quantum-mechanical approximation.

Van der Waals radii are thus an important part of the empirical basis of the force law. Such radii are well established for large angles χ to the bonding direction, but there is some dubiety as to their values at small angles. From the almost normal geometry of the molecules of simple derivatives of methane, Pauling deduced such a shortening of the radii at low angles as would remove non-bonding pressure at 35°. Dostrovsky, Hughes, and Ingold, accepting this conclusion, shortened their radii for angles below 90° by $0{\cdot}4(1 + \cos 2\chi)$ Å, thereby allowing the atoms a van der Waals surface which contracts towards the bonding direction, smoothly taking in Pauling's radius at 35°, and the covalent radius at 0°. For a semi-ionic halogen, the coefficient in the above formula was reduced from 0·4 to 0·2, because it would obviously be reduced to 0·0 in the free halide ion.

Whether or not this assumption of radii contracted at low angles is realistic, it had two convenient effects on the course of the calculations (its effect on their results is discussed below). For, first, it reduced to negligibly small values the non-bonding energies calculated for initial states, thereby enabling energies of steric hindrance to be related to compression energies calculated for transition states only. Secondly, it reduced to negligibility the calculated compression energy of one transition state, *viz.*, that of the substitution involving the methyl radical; and since any experimental assessment of energies of steric hindrance can only be relative, with the case of methyl as an adopted zero, it is convenient to have this energy for the methyl group calculated as zero. The overall simplifying effect was that energy of steric hindrance, though in principle to be calculated as a second difference of the compression energies of four states, could in practice be identified with the compression energy of the relevant transition state only.

Dostrovsky, Hughes, and Ingold estimated the lengths r_t of the semi-bonds to bromine in their transition states by two methods. The first had only intuitive justification, and gave 2·31 Å: compression energies were for the most part calculated with this value. Subsequently, the length was recalculated on the more rational group of assumptions that the energy of activation consists of the energy needed (1) to bring the three preserved C_α-bonds into a plane, (2) to remove solvating solvent displaced by the attack of the bromide ion, (3) to press the latter against the carbon atom to a nuclear separation r_α, (4) to stretch the CBr-bond to an equal length r_α, and (5) to divide the ionic charge equally between the bromine atoms, this last term being negative. It was assumed that energies (1) and (2) vary negligibly with r_α in the relevant range, that energy (5) passes through a stationary value (maximum resonance) at the transition-state distance, that (3) can be calculated as already outlined, and that (4) is given by the Morse function. The total energy was found to be minimal when r_α was 2·25 Å, this being the revised value of the semi-bond length r_t. The calculations were not systematically repeated with this not much altered value, but they were extended in a way which employed it, and, in the extension, the involvement of two slightly different values led to certain minor inconsistencies.

(b) *Effect of Steric Pressure on the Geometry of Transition States.*—Undoubtedly the most dangerous of the above assumptions is that summarised in the term " stiff " as applied to this model, particularly with respect to transition states, in which the important non-bonding pressures are developed. It cannot be true that bonding forces alone determine

the bond lengths and angles, and that then non-bonding forces build up steric energy within the model so determined. They must deform the model, raising the bonding energy and lowering the non-bonding, but in such a way that the total energy is minimised. The effect of the deformation will be to reduce the steric energy, now considered as the excess of total energy, bonding plus non-bonding, above what it would have been in the absence of the non-bonding forces.

To calculate minimised total energy in a transition state, with allowance for the possible bending and stretching of every bond that might be so affected, would be an arduous task. But most of the relief by deformation from non-bonding strain must come from the bending and stretching of the weak semi-bonds, and an energy calculation which allows for this is not unduly tedious. For convenience, we may call the transition-state model in which all degrees of freedom of deformation are permitted in the reaction system, the " plastic " model, even though it allows only the leading elements of the total plasticity of the natural transition state.

In the extension of their calculations mentioned above, Dostrovsky, Hughes, and Ingold contributed a little to the problem of calculating with the " plastic " model. When, as in general, the semi-bonds are both bent and stretched by non-bonding pressures, the bending will usually have a considerably more important energetic effect than the stretching. However, they then saw no easy way to compute the effect of bending. But in the substitutions of the trigonal molecules, methyl bromide and *tert.*-butyl bromide, there is no bending of the semi-bonds of the transition states, and their stretching could be, and was, taken into account by simply adding one more term, the non-bonding energy expressed as a function of r_α, to the five previously assumed to compose the activation energy. For methyl bromide there was no non-bonding energy in the transition state, and therefore no stretching of the semi-bonds, and no change of total energy. For *tert.*-butyl bromide, non-bonding compressions stretched the semi-bonds of the transition state by 0·04 Å, and reduced the total energy, and therefore the steric energy, by 0·3 kcal. mole^{-1}.*

The most notable case in which the calculated steric energy was obviously too high was that of *neo*pentyl bromide, the discrepancy amounting to about 7 kcal. mole^{-1}, of which about 1 kcal. mole^{-1} was ascribed to a polar effect. Although bending must occur here, the effect was calculated of allowing the semi-bonds to stretch, but not to bend; and it was found that this reduced the calculated total energy by 1 kcal. mole^{-1}. It was then suggested that an allowance for bending, if one were made, might absorb the major part of the remaining discrepancy of 5 kcal. mole^{-1}, the intuitive reasoning being that, as bending frequencies in molecules are often about one-half of the corresponding stretching frequencies, one might expect the energetic effect of bending to be roughly four times that of stretching, *i.e.*, about 4 kcal. mole^{-1} in this case.

This seems to have been not a bad guess, to judge from the results, reported in Section C, of our more recent calculations of the bonding and non-bonding energies of transition states as functions of all the degrees of freedom allowed in the " plastic " model. But, before coming to this, two other features of the earlier calculations require reconsideration.

(c) *Forms of the Non-bonding Force Law.*—Dostrovsky, Hughes, and Ingold chose an exponential form of steric interaction energy, $be^{-r/a}$, because theory indicates that the true expression should contain an exponential factor, and because an exponential function, with empirically determined parameters, is a notoriously powerful absorbent of errors arising from neglected power terms and factors; and certainly higher-power terms of electrostatic and electrokinetic types, as well as power factors of steric type, are neglected in their expression for the non-bonding energy. Born and Mayer had shown that the exponential potential combined as necessary with just the leading electrostatic and electrokinetic terms, gives a good account of energy–volume relations in simple ionic crystals (*Z. Physik*, 1932, **75**, 1), and Buckingham that it does the same for those of non-ionic gases and crystals (*Proc. Roy. Soc.*, 1938, *A*, **168**, 264), as has been extensively confirmed by this

* The different figures previously tabulated involve an inconsistency arising from the two estimates of the undeformed semi-bond lengths. But Fig. 6 of the previous paper shows fairly well the basis of the figures here cited.

author and by others subsequently. In the meantime, Westheimer has used the exponential form in successful calculations on a rate process, albeit a physical one, inasmuch as no bonds are formed or broken, *viz.*, the racemisation of 2 : 2′-dihalogenodiphenyl compounds (*J. Chem. Phys.*, **1947**, **15**, 253; Reiger and Westheimer, *J. Amer. Chem. Soc.*, 1950, **72**, 14).

However, it is well known that a power-law repulsive potential, of the form $b'r^{-n}$, with $8 \leqslant n \leqslant 14$, is about equally successful in the description of gaseous energy–volume relations; according to Buckingham (*loc. cit.*), any value of n within the limits indicated, if combined with a suitable value of b', will serve for this purpose. A. G. Evans took n as 9, when he calculated non-bonding energies with the expression $W = -Ar^{-4} + b'r^{-9}$, where the first term is electrostatic, and b' is evaluated from the condition that $dW/dr = 0$ at the van der Waals distance (*Mem. Proc. Manchester Lit. Phil. Soc.*, 1947, **87**); though had the omitted electrokinetic term been included, the value of b' would have been considerably altered.

In order to exemplify the effect of changing over to a power-type force-law, we have repeated Dostrovsky, Hughes, and Ingold's calculations for the bromide-ion substitution of methyl and *tert.*-butyl bromides, using, as they did in these especially simple cases, the " plastic " model, but assuming Evans's form of non-bonding potential, with the exception that we have included the leading electrokinetic term, and have redetermined b' accordingly. In these particular illustrative calculations, Dostrovsky, Hughes, and Ingold's assumptions concerning van der Waals radii have not been changed.

For the reaction of methyl bromide, the energy of the transition state, expressed as a function of r_α, is

$$W = C - 158r_\alpha^{-4} - 810r_\alpha^{-6} + 63{,}740r_\alpha^{-9} + 70{\cdot}6\left[e^{-3{\cdot}28(r_\alpha - 1{\cdot}91)} - 2e^{-1{\cdot}64(r_\alpha - 1{\cdot}91)}\right]$$

in kcal./mole, when r_α is in Å. The constant C can be allowed to determine any convenient energy zero. This energy is minimal when $r = 2{\cdot}45$ Å. Thus the new semi-bond length r_t is 0·2 Å greater than before. There is no significant non-bonding energy in either the initial or the transition state, and hence no energy of steric hindrance.

For the reaction of *tert.*-butyl bromide, there is still no significant non-bonding energy in the initial state. However, the energy of the transition state is raised by non-bonding pressures, one effect of which is to lengthen the semi-bonds. The additional energy, which must now be calculated with the power-type potential, includes, in the first place, six C_β–Br compression terms, each equal to

$$C_C - 39{\cdot}5r_C^{-4} - 708r_C^{-6} + 17820r_C^{-9}$$

where r_C is the common C_β–Br distance, a geometrically determinate function of r_α, and C_C is a constant, whose inclusion sets the energy zero of these terms at the point at which r_C is the appropriate van der Waals distance, 3·04 Å. The rest of the non-bonding energy consists of six H_β–Br compression terms, each equal to

$$C_H - 17{\cdot}8r_H^{-4} - 346r_H^{-6} + 7964r_H^{-9}$$

where r_H is the shortest H_β–Br distance, also a calculable function of r_α, and C_H similarly sets the zero of these terms where r_H is the van der Waals distance, here 2·98 Å. The reason why these energy zeros should be taken at the van der Waals distances is explained in the former paper. No larger H_β–Br distances lead to significant contributions to the energy. When these two sets of six terms are re-expressed as functions of r_α, and then added to the previous expression for W, a new function W is derived, which has its minimum at $r = 2{\cdot}53$ Å. The semi-bonds have thus been lengthened, by 0·08 Å, by the steric pressure. The new minimum lies 2·8 kcal. mole^{-1} above the old minimum. And since the old minimum included no non-bonding energy, and the initial states are calculated to have none, 2·8 kcal./mole represents the energy of steric hindrance of the reaction of *tert.*-butyl bromide.

From their exponential-type potential function, Dostrovsky, Hughes, and Ingold calculated 2·5 kcal. mole^{-1} as the energy of steric hindrance of this reaction.* The unimportant difference between these two estimates exemplifies the general point that the results

of such calculations are strongly buffered against even considerable variations in the assumed potential function, provided that this is one of those known to give a good description of physical properties, and provided that it is made as dependent as possible on empirical parameters. What has happened in the present illustration is that the stronger repulsive forces assumed in the Evans-type potential have further lengthened the semi-bonds; and this geometrical change has further reduced the non-bonding pressures on the bromine atoms by approximately as much as the stronger repulsions would have further increased them had the geometry remained unchanged.

Other trials which we have carried out with generally similar results involve retaining the exponential form of potential, but making it steeper or less steep by changing the length-constant in the exponent. However, we can give a single combined illustration of this and of another matter, which is considered in the next sub-section.

(d) *Angular Dependence of van der Waals Radii.*—As mentioned above, some doubt can be entertained as to whether these radii should be shortened at low angles to the bonding direction. Suppose that we decide not to shorten them. Then almost all compressions will be considerably strengthened; and we shall find appreciable non-bonding energy in the transition state of the reaction of the methyl group, and also in all initial states, including that of the reaction of the methyl group. The energy of steric hindrance of the reaction of a higher alkyl group will now have to be derived, without short-cuts, as the second difference of the total energies of four states, *e.g.*,

$$\left(W_{t\text{-Bu}}^{\text{transition}} - W_{\text{Me}}^{\text{transition}}\right) - \left(W_{t\text{-Bu}}^{\text{initial}} - W_{\text{Me}}^{\text{initial}}\right)$$

Since there are four terms, and in each extra compression can produce the sort of compensation already illustrated, the total opportunity for compensation is considerable.

In illustration we cite a calculation involving an exponential type of potential function, in which, not only have the compressions been intensified by omitting to shorten the van der Waals radii at low angles, but also they have been further strengthened by reducing the length-constant in the exponent, and thus steepening the exponential function. Instead of Born and Mayer's empirical constant 0·345 Å, we now assume the figure 0·165 Å, adopted by Westheimer (*loc. cit.*) to represent the properties of a function computed by Bleick and Mayer by a method of quantum-mechanical approximation for the mutual repulsion of two helium atoms (*J. Chem. Phys.*, 1934, **2**, 252), Westheimer having employed this value in the potential function from which he derived hydrogen–bromine compression energies in the work cited above.† When using this potential function for computing hydrogen–bromine compressions, we set the energy zero at 3·15 Å, and when using it for carbon–bromine compressions, we change the minimum to 3·55 Å, these being the unreduced values of the respective van der Waals distances.

With these assumptions, the semi-bond length in the transition state of the methyl reaction becomes 2·55 Å: the steeper repulsive potential, and the greater range of repulsion, have lengthened it by 0·3 Å. The extra compression in the transition state of the *tert.*-butyl reaction lengthens it by a further 0·1 Å. The excess of total energy due to the presence of compression in the transition state of the *tert.*-butyl reaction is greater than the corresponding excess in the transition state of the methyl reaction by 5·4 kcal./mole. But the extra energy due to compression in the initial *tert.*-butyl bromide molecule exceeds that in the initial methyl bromide molecule by 2·7 kcal. mole^{-1}. It follows that the energy of steric hindrance of the *tert.*-butyl substitution is 2·7 kcal. mole^{-1}, in substantial agreement with the other estimates.

The general conclusion we draw from exploratory calculations such as have been illustrated, is that, in seeking to extend the work of Dostrovsky, Hughes, and Ingold, there is little to be gained from making changes in any of their assumptions of whose physical accuracy we are still uncertain, except the change which involves going over completely from the " stiff " to the " plastic " model.

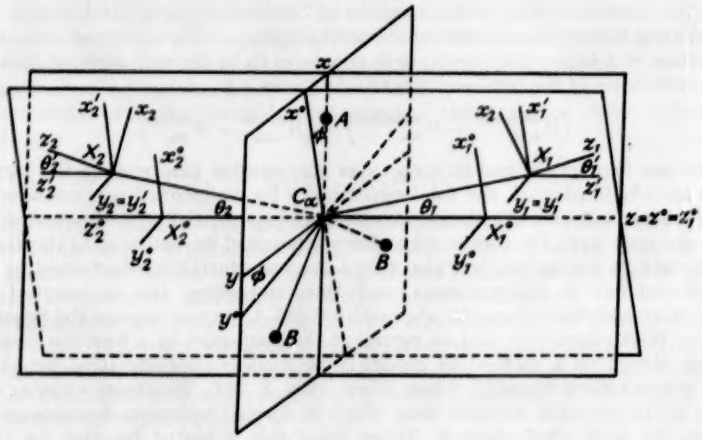
* Corrected for the inconsistencies mentioned in the preceding footnote.

† We should not have assumed, however, that Born and Mayer's length constant, appropriate for compressions involving halide ions, would be applicable to the hydrogen–hydrogen repulsions discussed by Barton (*J.*, 1948, 340).

(B) Methods of Calculation.

In the energy calculations we have in principle, and in the entropy calculations in practice, to treat the transition and the initial states differentially. We must therefore adopt the " plastic " model for both states. In each, it permits every possible form of plasticity to the system of actually or potentially reacting atoms, but in the remainder of the alkyl groups it allows only conformational rotations, and not either bond-stretching or bond-bending. This model is, of course, a large advance on the " stiff " model; but it still involves the approximation of assuming that intra-alkyl deformation is not available to replace some of the non-bonding energy by a smaller amount of bonding energy; and of assuming also that, if the entropy associated with intra-alkyl vibrations is not negligible, at least the change which such entropy undergoes when a transition state is formed is negligible. This neglect of deformation in the alkyl groups, except at the reaction centre, is probably the biggest single source of error in the present work.

Fig. 1. *Co-ordinate system for transition states.*



(a) *Energy of the " Plastic " Model of the Transition and the Initial States.*—As regards the transition state, the main part of the energy problem is to calculate the total, bonding plus non-bonding, energy of the system of atoms concerned over a range of configurations, permitted by the model, and so chosen that it includes the configuration of the transition state. The calculation has not to be made absolute with respect to a physically prescribed zero, but in principle the zero of energy is that of the undeformed initial state. The first purpose for which this energy–configuration function is needed is in order to minimise it, thereby deriving both the geometry and the energy of the transition state. But the further purpose is to be kept in view of computing the entropy of the transition state, and this requires a knowledge, not only of its geometry, but also of the variation of its energy with configuration over a small range of configurations about that of the transition state.

The first proceeding is to choose axes fixed in the atomic assembly, and it is convenient to do this sufficiently comprehensively, as shown in Fig. 1, for use in all the steps of calculation mentioned. We shall have to describe both positions and displacements. For position axes, we take an origin at C_α, and the plane containing the three bonds from C_α to hydrogen or carbon as the *xy*-plane, one of the three bonds, the unique one if there is such, marking the *x*-axis: the directions of the *y*- and the *z*-axis then follow from the right-hand rule. The halogen atoms are assumed to lie symmetrically about the *xy*-plane. This will certainly be true for all transition states, except possibly those of the *iso*butyl group, for which we assume it nevertheless, because of the difficulty of making definite, and of working with, any other assumption. In the absence of non-bonding pressures,

the halogen atoms will lie on the z-axis, and certain resultant non-bonding pressures will leave them on that axis; but other resultant pressures will move them off this axis by some angle θ, leaving them still in the zx-plane; and yet others will shift them off that plane on to another derived from it by rotation about z by some angle ϕ. This rotation can be taken as defining new position axes, x°, y°, z° $(= z)$; and the halogen positions can alternatively be expressed in polar co-ordinates r, θ, ϕ, having the usual relation to x, y, z. We require axes for the description of displacements of the halogen atoms, relatively to the rest of the atomic system, from their energy-minimised positions. For the general case, which it is always possible to specialise, we take them as lying in, or perpendicular to, the $z^\circ x^\circ$-plane, but with origins at the halogens X_1 and X_2. If we first set up for X_1, displacement-axes x_1', y_1', z_1', parallel to the position axes, and for X_2 a similar, but left-hand set, x_2', y_2', z_2', derived from the X_1-set by reflexion in the xy-plane, it is found that the normal displacements are rotated in the $z^\circ x^\circ$-plane with respect to these axes by some angle θ', and it is therefore convenient to take displacement co-ordinates in these rotated directions, x_1, $y_1(= y_1')$, z_1 for X_1, and x_2, $y_2(= y_2')$, z_2 for X_2.

The undeformed initial state is our energy zero, but we have to compute energies of deformation of the alkyl halide, first, as will be explained below, in connexion with the calculation of the excess of energy in the transition state, and, secondly, for the purpose of calculating the entropy of the initial state.

Axes set in the initial alkyl halide molecule are therefore chosen as shown in Fig. 2. For the description of position, the origin is at C_α, and the halogen X_1 lies on the z-axis. This defines an xy-plane, on which the three bonds from C_α to hydrogen or carbon can be projected, the projection of one of these bonds, the unique one if there is such, defining the x-axis, and the right-hand rule the y-axis. For the description of displacements of the halogen relatively to the alkyl group, axes x_1, y_1, $z_1(= z)$, with an origin at X_1, are taken parallel to the corresponding position axis.

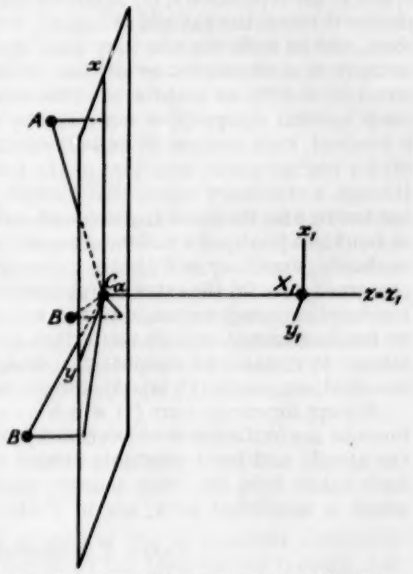


FIG. 2. *Co-ordinate system for initial states.*

The first step in the calculation of the energy–configuration function for the transition state is the simplifying one of determining, for each alkyl group, the angle ϕ: for the plane $z^\circ x^\circ$ thereby defined is to contain the halogens in the transition state, and hence a survey of the energy variation as the halogens move over this plane will provide a function, which, by minimisation, locates the transition state. In some cases it follows from symmetry that ϕ either may, or must, be taken as zero. In other cases ϕ can easily be determined, starting from the results which Dostrovsky, Hughes, and Ingold calculated with bromine as their halogen, or from similarly calculated results for chlorine and iodine. For it is essentially a question of finding the azimuth ϕ of the resultant non-bonding force on a halogen atom, initially placed on the z-axis at the point calculated by those authors, or by their method; and that, in turn, follows by vector summation of the individual atom-pair forces, which was computed by them for bromine, and may be similarly computed for chlorine and iodine. The correction which would allow for the curvature of the resultant force, as the halogen moves to its new position, turns out to be hardly worth making; and the results for chlorine, bromine, and iodine are so nearly identical that we can, with sufficient accuracy, adopt common values, as shown in Table 1.

In the problem of tracing the changes of total energy W over varying halogen co-ordinates in the $z^\circ x^\circ$-plane, it is convenient to work at first in the polar co-ordinates r, θ.

For any particular pair of such co-ordinates, the procedure is to build up the configuration having them from the undeformed initial state in a series of steps, and to sum the corresponding energy changes. The energy of activation is thus described as the algebraic sum of eight terms, *viz.*, the energy needed (1) to bend the C–Br bond of the initial molecule from the *z*-direction through an angle θ assumed small, (2) to bend the other C_α bonds

TABLE 1. *Determination of the plane containing transition-state halogen.*

Alkyl group	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
Bond defining x	$C_\alpha H_\alpha$	$C_\alpha C_\beta$	$C_\alpha H_\alpha$	$C_\alpha C_\beta$	$C_\alpha C_\beta$	$C_\alpha C_\beta$	$C_\alpha C_\beta$
Angle ϕ	0°	11°	0°	0°	11°	0°	21°

into the *xy*-plane, (3) to remove enough solvent sufficiently far from the reacting particles to permit their interaction, (4) to force the halide ion against the α-carbon atom at the angle θ, and to the separation r, (5) to stretch the C–Br bond to the length r, (6) to divide the ionic charge between the halogen atoms, (7) to release any non-bonding pressures in the initial state, and (8) to do the necessary work against such pressures exerted on the halogen atoms in the (r, θ)-configuration by all other atoms in the system except the α-carbon atom. The terms (6) and (7) are negative, and the other terms positive. The simplifying assumptions made are that energy (1) is controlled by a simple harmonic potential for the small angles θ involved, that energies (2) and (3) can be treated as independent of r and θ, as also can (6) for configurations near that of the transition state, about which this term must pass through a stationary value, that energies (4) and (5) may be treated as dependent on r, but not on θ for the small angles considered, although energies (7) and (8) must be computed as functions jointly of r and θ. The constant terms (2), (3), and (6) need not be calculated explicitly, since they will always cancel in the energy differences with which we shall be concerned, *viz.*, (*a*) the extra energy conferred on undeformed transition states by increased non-bonding compressions, directly, and through their effect on configuration and hence on bonding energy, and (*b*) the further energy which transition states acquire by deformation. It remains to compute the configuration-dependent terms for a suitable (r, θ)-manifold, *viz.*, terms (1), (4), (5), and (8), as well as the initial-state-dependent term (7).

Except for energy term (1), which is a new feature in these calculations, all the necessary formulæ are in the paper of Dostrovsky, Hughes, and Ingold, who also cited the sources of the atomic and bond constants needed for their application. The constants, which we have taken from the same sources, except for some revised frequencies, the source of which is mentioned later, are in Table 2. The non-bonding energy formulæ contain

TABLE 2. *Adopted atomic and bond constants.*

Z	$[R]$ (cm.^{3} mole^{-1})	$\mathscr{I}$ (ev)	ρ_W (Å)	D (CZ) (kcal. mole^{-1})	ν(CZ) (cm.$^{-1}$)	r_0 (Å)
C	2·41	12·0	1·6	—	—	1·54
H	1·09	14·5	1·2	—	—	1·09
Cl	5·9	12·2	1·8	80	732	1·76
Br	8·8	10·5	1·95	67	611	1·91
I	13·7	9·5	2·15	53	533	2·10
Cl^-	8·7	9·5	1·81	—	—	—
Br^-	12·2	9·0	1·95	—	—	—
I^-	18·5	8·7	2·16	—	—	—

the polarisability α, and the ionisation potential $\mathscr{I}$, of the atoms concerned, the former following from the refraction constant R by multiplication by $3/4\pi N$. For the ionisation potential of the iodide ion, we had no direct source, and the figure entered in the Table is the one we assumed, after a survey of other values applying to bound and ionised halogens. For the polarisabilities and ionisation potentials of semi-bound semi-ionic halogens, we took means between corresponding values for the bound halogen atoms and the halide ions. The non-bonding energies also depend on the effective van der Waals radii ρ_W of the atoms involved, and, for obtuse angles χ to the bond direction, these were taken equal to the maximum radii ρ_W given in the Table, but for acute angles were reduced from these maxima by $0{\cdot}4(1 + \cos 2\chi)$ or $0{\cdot}2(1 + \cos 2\chi)$ Å, as already explained. The bonding-energy formula contains the dissociation energy D, the stretching frequency ν, and the length

r_0 of the bond. For the first two of these quantities, we took methyl halide values, because the Morse formula used is designed for application to diatomic molecules, and the methyl halides are the only alkyl halides in which the halogen-stretching vibrations are sufficiently free from intramolecular coupling to permit of treatment on this basis, which we have to make self-consistent.

Of the many bending potential functions V which might have been employed for the calculation of the energy term (1), the simplest is that given by Cross and van Vleck (*J. Chem. Phys.*, 1933, **1**, 356) as a result of their valency-force treatment of the vibrations of ethyl chloride, bromide, and iodide. For here, the total energy associated with the bending of a CCHal-angle is expressed as a function of the change $\Delta\gamma_C$ in that angle only, although other valency angles must change with it for obvious geometrical reasons :

$$2V = K_C(\rho^2_{CC} + \rho^2_{CHal})\Delta\gamma_C^2$$

The values of K_C, the bending force-constant, are in Table 3. We have used this function whenever posible, *i.e.*, except for methyl halides, y-bending in primary alkyl halides, and x-bending in the *iso*propyl halides (see Figs. 1 and 2). For these deformations, we require energy as a function of the change $\Delta\gamma_H$ of HCHal-angles, and for this we took the square-term part of the bending-potential function of Crawford and Brinkley (*J. Chem. Phys.*, 1941, **9**, 69). In this function, which may be expressed in the form,

$$2V = k_H(\rho^2_{CH} + \rho^2_{CHal})\ \Sigma\Delta\gamma_H^2$$

all the geometrically related angular changes are considered to make their own contributions to the energy of deformation, and the bending force-constant k_H applies to each such change, so that a sum must be taken. The values of k_H are in Table 3. The application of this equation to the methyl halides is straightforward, but its application to y-bending in primary alkyl halides, and to x-bending in *iso*propyl halides, involves the approximation of assuming that, in these deformations, the CCHal-angles, the changes in which are small relatively to the changes in the HCHal-angles, so that they contribute but little to the energy, can with sufficient accuracy be treated as though they were HCHal-angles.

TABLE 3. *Adopted values of bond-bending force-constants.*

	RCl	RBr	RI
10^5K_C (with K_C in dyne cm.$^{-1}$)	0·22	0·22	0·18
10^5k_H ,, k_H ,, ...	0·16	0·13	0·10

For each point r, θ in the selected manifold of each of the 21 reactions considered (7 alkyl groups and 3 halogens), the calculation described has been carried through, but only with respect to the configuration-dependent energy terms (1), (4), (5), and (8); because the inclusion of the initial-state term (7) in the programme is a formality. For Dostrovsky, Hughes, and Ingold showed that, by the method of calculation which they used, the compression energy in all initial states is either zero, or, when compared with the compression energy of corresponding transition states, is too small to be worth taking into account. The present extension of their method cannot change that conclusion. So, for each reaction, the energies (1), (4), (5), and (8), calculated for each r, θ, are added, and the totals are plotted as a surface over the co-ordinate plane $z^\circ x^\circ$. Each surface has the form of a basin, the lowest point in which gives the configuration and energy of the transition state.

These results are illustrated and tabulated in Section C, where also they are discussed in relation to kinetic observations.

(b) *Entropy of the "Plastic" Model of the Transition and the Initial State.*—In the transition-state theory, reaction rate depends on the proportion of molecular systems maintained in the transition state, and therefore, not only on the energy difference between the initial and the transition state, but also on the ratio of their statistical probabilities of occupation, and thus on its logarithm, the entropy difference. For any overall state, the probability is given by a Boltzmann-weighted count of the individual energy-states included in it, the weighting factor making lower-lying energy-states more important in

the count. We shall assume that the total wave-function can be so factorised that each vibrational state carries with it a similar set of rotational states, each of which in turn carries a similar set of translational states, the total number of energy states being therefore the product of the numbers of vibrationally, rotationally, and translationally, distinctive kinds of states, and the total entropy the sum of the vibrational, rotational, and translational entropies. We have to deal with reaction in solution, and shall assume further that the transition state, and each species composing the initial state, behave as ideal solutes. And on this basis we shall calculate, for the adopted model, the entropies of the transition and initial states, at a standard concentration, 0·0446M, and a standard temperature, 298·1°K. The particular standard of concentration chosen (which corresponds to an ideal osmotic pressure of 1 atmosphere) is of no importance: at another concentration, all the calculated entropies would be changed by a constant amount, and so the differences, in which alone we are interested, would be unaltered. The adopted temperature is within the general range of our experimental investigations: a change to another temperature would produce non-uniform changes in the entropies; but the effect on the entropy differences of a change to another temperature within our range would be quite small.

The formula for translational entropy derives from the quantal theorem of the particle-in-a-box, and the only molecular quantity involved is the mass of the particle, heavier particles having more low-lying energy levels than lighter. For our purposes the equation may be reduced to the form,

$$S_t = 2{\cdot}303\boldsymbol{R}(1{\cdot}5 \log M + 2{\cdot}5 \log T) - 2{\cdot}315$$

cal. deg.$^{-1}$ mole^{-1}, at the standard concentration, or

$$S_t = 2{\cdot}303\boldsymbol{R}(1{\cdot}5 \log M) + 0{\cdot}515$$

cal. deg.$^{-1}$ mole^{-1}, at the standard concentration and temperature. Here the constant term is so adjusted that the mass M is simply the chemical molecular weight.*

At once we see a factor which will tend to make higher homologues react more slowly, independently of the position of the extra mass in the higher homologue, and therefore independently of any question of steric hindrance. The entropy of activation $S^{\ddagger}$ is the entropy S of the transition state XRX^-, minus the sum of the entropies S of the components RX and X^- of the initial state; † so that for the translational contribution, we have

$$S_t^{\ddagger} = S_t(XRX^-) - [S_t(RX) + S_t(X^-)]$$

The translational entropy of X^- is, of course, constant from one alkyl group to another. However, in a higher homologue, the masses of XRX^- and of RX are increased by the same amount; and so, because the former mass is larger to start with, it will be increased in smaller ratio than will the latter; and since, for the entropy, it is the logarithm of the mass that matters, $S_t(XRX^-)$ will be increased less than will $S_t(RX)$, with the result that the translational entropy of activation $S_t^{\ddagger}$ will be lowered.

The calculation of rotational entropies is derived from the quantal problem of the rotor, the energy levels of which are lowered and concentrated by increasing the moments of inertia, though some energy states may disappear when symmetry causes certain rotations to make no physical difference. For our purposes the equation may be reduced to

$$S_r = 2{\cdot}303\boldsymbol{R}(0{\cdot}5 \log ABC - \log \sigma + 1{\cdot}5 \log T) - 5{\cdot}384$$

cal. deg.$^{-1}$ mole^{-1}, or, at the standard temperature,

$$S_r = 2{\cdot}303\boldsymbol{R}(0{\cdot}5 \log ABC - \log \sigma) - 3{\cdot}686$$

* Here and later, constant terms in expressions for entropy are calculated with Birge's 1939 values of the universal constants, $\boldsymbol{k}$, $\boldsymbol{h}$, and $\boldsymbol{N}$.

† For convenience in this paper, we simplify the standard symbols $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$, down to $S^{\ddagger}$ and $H^{\ddagger}$, for entropy and heat of activation, thus allowing ‡ to be, not only the label of a process, but also the operator which takes a difference over it. This is because we have needed Δ as the operator for taking another kind of difference, that which attends the replacement of methyl by a higher alkyl group. We are concerned with both kinds of first difference, *e.g.*, ΔS and $S^{\ddagger}$, as well as second differences, *e.g.*, $\Delta S^{\ddagger}$, which in our equations signifies the constitutional increment in the entropy of activation.

cal. deg.$^{-1}$ mole^{-1}. Here A, B, and C are the principal moments of inertia, σ is a symmetry factor, and the value of the constant term is so fixed that A, B, and C are to be calculated in atomic-weight-square-Ångström units.

We find here a constitutional effect on rotational entropy, and hence on entropy of activation, and on reaction rate, which, even though it depends on the position of an added mass, is not an effect of steric hindrance, though, still more easily than the translational entropy effect, it might be mistaken for such. The rotational entropy of activation is given by the difference

$$S_r^{\ddagger} = S_r(\mathrm{XRX}^-) - S_r(\mathrm{RX})$$

since the rotational entropy of the halide ion may be taken as zero. This part of the entropy of activation is always positive, because the mass added to the original molecule in the formation of the transition state must increase at least one, and cannot decrease any, moment of inertia, and any disturbance due to symmetry, even if non-uniform, will be too small to make a difference. Now we can show that an inert mass, added to the original molecule by a structural change, may either increase or decrease the rotational entropy of activation, according as the added mass is sufficiently far away from, or sufficiently near to, the reaction centre. The reason for the positional distinction is that, in the former case, the centre of gravity moves away from, and, in the latter, it moves towards, the point at which mass is being increased in the formation of the transition state.

A formal proof could be given, but is intricate, and a simple numerical illustration is easier to follow. Let the original molecule be represented by two unit masses, A and B, unit distance apart, A being the reaction centre; then its moment of inertia will be 1/2. Let a transition state be formed by the addition of a reagent of unit mass at A; then its moment of inertia will be 2/3, a proportional increase of 4/3, so that the rotational entropy of activation, except for a constant term, will be proportional to log 1·33. Now suppose that we add to the original molecule another unit of mass at B; then the moment of inertia of the molecule will become 2/3, and that of the transition state 4/4, a proportional increase of 3/2, so that the rotational entropy of activation, apart from the constant term, will be proportional to log 1·5, *i.e.*, it will be larger than before. But suppose that, instead of adding the extra mass at B, we had added it at A; then the moment of inertia of the molecule would still be 2/3, but that of the transition state would be 3/4, a proportional increase of 9/8, so that entropy of activation, except for its constant part, would be proportional to log 1·125, *i.e.*, less than if the extra mass had been added at B, and even less than if it had not been added at all.

In purely aliphatic molecules, the simple distinction illustrated is subject to a bias in favour of the effects expected from substitution near the reaction centre, because of the non-linearity of the carbon chains. We have now three moments of inertia to take into account: even an ω-extension of a non-acetylenic chain is usually not far enough away from any principal axis of inertia to produce a positive differential, from the initial to the transition state, in the factors of increase of the corresponding moment of inertia, which can counteract the effect of the proximity of the extension to another principal axis in producing a negative differential in the factor of increase of another moment of inertia. The result is that even ω-extension will usually decrease the rotational entropy of activation, whilst α-branching will decrease it more strongly. Thus the general effect of rotational entropy, like that of translational entropy, is in the direction of making higher homologues react more slowly; and rotational entropy has the further peculiarity that its retarding influence comes out most strongly with α-branching, just as if the effect were one of steric hindrance; with which it has actually nothing to do, since any bulk that might be associated with the added mass has not yet been taken into account. Isotopic substitution by a heavier isotope at different points along the carbon chain, where there would be a mass change without a volume change, would show the effect described.

Our calculations of rotational entropy involve some approximations arising from the model employed, a simplified one, which allows for conformational rotation, but not for bond-stretching and -bending, within the alkyl groups. We have therefore assumed that

conformational rotation will combine with overall rotation in the relevant region of temperature, and have calculated symmetry numbers accordingly. In the cases of the *n*-propyl and *iso*butyl halides, we were in the difficulty of not knowing which conformations are predominant, and to what extent. We decided that the procedure which would be most faithful to the model, and would at the same time act as an insurance against an error of the magnitude which might be incurred through the assumption of a wrong conformation, would be to calculate, in each such case, entropies for all conformations, and take the average. There are, of course, three, the *anti*-, and the *D*- and *L*-*syn*-conformations, designated always with reference to the unique groups attached to the β- and the α-carbon atom. Since the calculations here reported were finished, Brown and Sheppard have shown spectroscopically (*Trans. Faraday Soc.*, 1954, **50**, 1164) that both *anti*- and *syn*-conformations are present in comparable amounts in liquid *n*-propyl chloride, bromide, and iodide, and in *iso*butyl chloride. But we still do not know the proportions, though it seems fairly certain that in liquid *iso*butyl chloride the *syn*-conformation is in distinct excess, perhaps an excess not far removed from the 2 : 1 excess which our calculations assume.

The calculation of vibrational entropy proceeds from the quantal problem of the harmonic oscillator. Normal vibrations being, by definition, independent of each other, the total number of vibrational energy levels is the product of the numbers of those of each normal vibration; and thus, each of the $3n-6$ normal vibrations of an *n*-atomic non-linear molecule, or the $3m-7$ vibrations of an *m*-atomic transition state, makes its own contribution to the vibrational entropy, so that a sum has to be taken. The lower a fundamental frequency, the more concentrated will be the energy levels of its vibration, and the greater will be the entropy contribution of the latter. The formula for vibrational entropy is

$$S_v = \sum_{\text{vibs.}} [-R \ln (1 - e^{-x}) + Rxe^{-x}/(1 - e^{-x})]$$

where $x = h\nu/kT$, ν being the vibration frequency in sec.$^{-1}$. At our standard temperature, $x = 0{\cdot}00483\omega$, where ω is the vibration frequency in cm.$^{-1}$.

Our model involves the assumption that all intra-alkyl vibrations are large enough to be unexcited, so that their entropy contribution is zero in both the transition and the initial state, leading to a difference of zero, as their contribution to the vibrational entropy of activation. Of course, the vanishing individual entropies are unrealistic; but we hope that intra-alkyl vibrations will make such similar contributions to the vibrational entropy in the transition and the initial state that the differences of these contributions, if not zero, will be small, and, what is more important to us, the differences between these differences, from case to case, will be quite small.

The serious part of our calculation of vibrational entropies is therefore that concerned with the actual or potential reaction centres. We have to determine the fundamental frequencies of the systems of atoms concerned. In the transition state, the system has 5 vibrations, whose normal co-ordinates are sufficiently distinguished by the displacements of the halogen atoms (see Fig. 1). They are $z_s = z_1 + z_2$, $x_s = x_1 + x_2$, $y_s = y_1 + y_2$, $x_a = x_1 - x_2$, and $y_a = y_1 - y_2$, the sixth degree of freedom of the two halogen atoms, $z_1 - z_2$, being the reaction co-ordinate. The subscripts *s* and *a* signify that the first three vibrations are symmetric to the *xy*-plane, and that the last two are antisymmetric. In all five vibrations, the alkyl group undergoes translatory oscillations, if, and to the extent to which, this is necessary in order to hold still the centre of gravity; and in the last two vibrations it undergoes librations to the extent required to conserve angular momentum. In the trigonal transition states of the methyl and *tert*.-butyl groups, the vibrations x_s and y_s form a degenerate pair (Π_u, to the spectroscopist), and x_a and y_a form another such pair (Π_g, in his language). The other transition states involve no such degeneracies. In the trigonal transition states, the non-degenerate vibrations and the degenerate pairs belong to three different symmetry species. In the other transition states, there are four symmetry species, because z_s and x_s fall into the same species, while each of the other vibrations has its own species. The occurrence of two non-degenerate vibrations in the same species has

the consequence that their frequencies appear as the solutions of a quadratic equation, without any accompanying mathematical instruction for distributing the roots between the two normal co-ordinates.

Corresponding to these five vibrations of the transition state, and to the translational motion in the reaction path, the initial state will have three degrees of freedom of translation of the halide ion, with which we are not now concerned, together with three vibrations of the bound halogen atom relatively to its alkyl group. These vibrations may be distinguished by the displacement co-ordinates of the halogen atom (see Fig. 2), as z_1, x_1, and y_1. In the trigonal halides of methyl and *tert.*-butyl, the vibrations x_1 and y_1 form a degenerate pair (E, to the spectroscopist). In the other alkyl halides, all vibrations are non-degenerate. In all alkyl halides, each non-degenerate vibration, and each degenerate pair, has its own distinct species.

Reverting to the transition state, the starting point of our determination of its vibration frequencies, and thus of the vibration entropy, consists in the basin-shaped energy surfaces, calculated as described in the preceding sub-section. The limiting directions of the principal axes of the lowest contours of such a surface give the directions of the displacements, z_1, x_1, etc. (see Fig. 1), *i.e.*, they determine the angle θ', which is not the same as θ, unless both are zero. Sections of the surface, cut along these directions, yield curves, whose lowest portions, when approximated to parabolæ, give force-constants for the displacements z_1, x_1, etc., and hence the force-constant for the vibration z_s, and the bending force-constant of the two vibrations x_s and x_a. The bending force-constant we prefer to handle as a moment-constant, into which it may be converted by multiplication by the square of the distance of a halogen atom from the centre of its rotatory motion in the bending vibration concerned. We have not a sufficient background of energetic information systematically to compute the moment-constant governing the other two vibrations y_s and y_a. But for the methyl and *tert.*-butyl transition states, we know, from the trigonal symmetry, that this moment-constant will be exactly equal to the previous one; and for the other transition states we can make approximate estimates. Our estimates are based on the assumption that the moment-constant relevant to the vibrations y_s and y_a will be determined mainly by those attachments to C_α which have extension in the y-direction, *i.e.*, the system $BC_\alpha B$ in Fig. 1. Therefore, for the transition states of all primary alkyl groups, we take this moment-constant as equal to that of the transition state of the methyl group; and for the transition state of the *iso*propyl group, we take it as equal to the moment-constant of the transition state of the *tert.*-butyl group. Since the moment-constants of the transition states of the methyl and *tert.*-butyl groups differ by only 7%, so that their square roots, to which frequencies are proportional, differ by only 3·5%, it would seem probable that no large error is here involved.

The calculation of mass-factors for the frequency formulæ is a mechanical matter, except for the vibrations y_s and y_a of those transition states in which both hydrogen and carbon atoms are bound to C_α. Here, as already explained, we cannot follow logically the requirements of the model; and, since we cannot, it seems best to make the simplest available, reasonably realistic, approximations. For y_s in these cases, we assume that most of the oscillatory motion of the alkyl group will be centred in the α-carbon atom, which will carry its attached hydrogen atoms with it, leaving the heavier carbon attachments only negligibly disturbed. For y_a in the same cases, we assume that the libratory alkyl motion is concentrated in the $BC_\alpha B$-group (Fig. 1), and is so nearly pivoted about the $C_\alpha A$-bond, that the rest of the alkyl group is negligibly disturbed.

With these approximations, frequency formulæ for the transition states have been developed, which are of valency-field type, without cross-terms. It is to be noted that the so-called valency forces have to be taken along z_1 and z_2, and are therefore not centred at C_α, unless $\theta' = \theta$, which is never true, except when both are zero. Let f_s be the force constant for the vibration z_s in dyne cm.$^{-1}$, and let Δ_x be the moment-constant for the vibrations x_s and x_a, and Δ_y that for the vibrations y_s and y_a, in dyne cm. radian^{-1}. Let M, M_h, M_a, M_m, and M_p be the chemical molecular weights of the transition state, a halogen atom, the alkyl group, a methylene group, and a methine group, respectively. Let I_x, I_{hx}, I_{ax}, I_{mx}, and I_{px} be the moments of inertia, in atomic-weight-square-Ångström

units, of the transition state, a halogen atom, the alkyl group, the α-methylene group, and the α-*iso*propylidene group, respectively, about an axis parallel to x_0 through the centre of gravity of the transition state; and let I_y, I_{hy}, and I_{ay}, have corresponding meanings in relation to an axis parallel to y_0, through the centre of gravity. Let r_t be the length of a halogen semi-bond in Å. When $\Delta_x = \Delta_y$, $I_z = I_y$, $I_{hz} = I_{hy}$, or $I_{az} = I_{ay}$, we shall write either of the equal quantities as Δ_{xy}, I_{zy}, I_{hxy}, or I_{azy}, as the case may be. If $\mathbf{c}$ is the velocity of light, and if ω_{zz}, ω_{xz}, ω_{yz}, ω_{za}, and ω_{ya} are the frequencies in cm.$^{-1}$ of the vibrations z_z, x_z, y_z, x_a, and y_a, respectively, the formulæ giving these frequencies in the various transition states are as follows. For the methyl and *tert.*-butyl transition states, they are

$$4\pi^2\mathbf{c}^2\omega^2_{zz} = 2f_z\boldsymbol{N}/M_h$$

$$4\pi^2\mathbf{c}^2\omega^2_{xz} = 4\pi^2\mathbf{c}^2\omega^2_{yz} = 2\Delta_{xy}M\boldsymbol{N}/10^{-16}M_hM_ar_t^2$$

$$4\pi^2\mathbf{c}^2\omega^2_{za} = 4\pi^2\mathbf{c}^2\omega^2_{ya} = \tfrac{1}{2}\Delta_{xy}I_{xy}\boldsymbol{N}/10^{-16}I_{hxy}I_{axy}$$

For the ethyl, *iso*propyl, *n*-propyl, *iso*butyl, and *neo*pentyl transition states, the formulæ are

$$4\pi^2\mathbf{c}^2\omega^2_{zz} + 4\pi^2\mathbf{c}^2\omega^2_{xz} = \frac{f_z\boldsymbol{N}}{M_h}\left(1 + 2\frac{M_h}{M_a}\sin^2\theta'\right) + \frac{2\Delta_x\boldsymbol{N}\cos^2\theta'}{10^{-16}M_hr_t^2\cos^2\theta}\left(1 + 2\frac{M_h}{M_a}\cos^2\theta'\right)$$

$$4\pi^2\mathbf{c}^2\omega^2_{zz} \cdot 4\pi^2\mathbf{c}^2\omega^2_{xz} = 2f_z\Delta_xM\boldsymbol{N}^2\cos^2\theta'/10^{-16}M_h^2M_ar_t^2\cos^2\theta$$

$$4\pi^2\mathbf{c}^2\omega^2_{yz} = 2\Delta_y(2M_h + M_m)\boldsymbol{N}/10^{-16}M_hM_mr_t^2 \qquad \text{(not } \textit{iso}\text{propyl)}$$

$$,, \quad = 2\Delta_y(2M_h + M_p)\boldsymbol{N}/10^{-16}M_hM_pr_t^2 \qquad (\textit{iso}\text{propyl)}$$

$$4\pi^2\mathbf{c}^2\omega^2_{za} = \tfrac{1}{2}\Delta_xI_y\boldsymbol{N}/10^{-16}I_{hy}I_{ay}$$

$$4\pi^2\mathbf{c}^2\omega^2_{ya} = \tfrac{1}{2}\Delta_y(2I_{hz} + I_{mz})\boldsymbol{N}/10^{-16}I_{hz}I_{mz} \qquad \text{(not } \textit{iso}\text{propyl)}$$

$$,, \quad = \tfrac{1}{2}\Delta_y(2I_{hz} + I_{pz})\boldsymbol{N}/10^{-16}I_{hz}I_{pz} \qquad (\textit{iso}\text{propyl)}$$

Consistently with our model, we have calculated initial-state halogen frequencies under the assumption that the alkyl groups behave as vibrationless assemblies. This was in order to obtain vibrational entropies comparable with those similarly calculated for the transition states, so that errors due to non-rigidity in the alkyl groups, and consequent coupling between halogen and alkyl vibrations, would be largely self-compensatory in the differences representing vibrational entropies of activation.

As a basis of force-constants for halogen-stretching vibrations z_1 (cf. Fig. 2), we have used the observed, and securely assigned, halogen-stretching frequencies of the methyl halides, which cannot be disturbed by halogen-bending; and we have applied these force-constants to z_1 vibrations throughout. As source of the moment-constants for halogen-bending against hydrogen, we have taken the observed, and definitely assigned, halogen-bending frequencies of the methyl halides, which cannot be disturbed by halogen-stretching; and these moment-constants we have applied to all halogen-bending vibrations in which the main angular change is in HCHal-angles, *i.e.*, to the y_1 vibrations of all primary halides, and to the x_1 vibrations of *iso*propyl halides (cf. Fig. 2). As source of the moment-constants for halogen bending against carbon, we have used the observed, and equally well assigned, low bending frequencies of the ethyl halides, Cross and van Vleck's investigation having shown that these frequencies are very little disturbed by halogen stretching; and we have applied these moment constants to all halogen-bending vibrations in which the main angular change is in CCHal-angles, *i.e.*, to the x_1 vibrations of all primary alkyl halides, the y_1 vibrations of *iso*propyl halides, and the x_1 and y_1 vibrations of *tert.*-butyl halides.

For the derivation of force- and moment-constants of the initial state, we have chosen as our observational basis the frequencies of the methyl and ethyl halides, not only because these are the simplest sources to which we could have turned, but also because their use

is demanded by the requirement of consistency with our treatment of the vibrations of the transition state; for these same frequencies were employed, in Morse or harmonic functions, during the construction of the transition-state energy surfaces, and they are therefore at the basis of the force- and moment-constants, therefrom computed, by means of which the transition-state frequencies were calculated.

In the following frequency formulæ, we write f_z for the force-constant in dyne cm.$^{-1}$ for the vibration z_1, and Δ_x and Δ_y for the moment-constants in dyne cm. radian^{-1} for the vibrations x_1 and y_1 respectively. We also write M, M_h, and M_a for the chemical molecular weights of the alkyl halide, the halogen atom, and the alkyl group, respectively, I_x, I_{hx}, and I_{ax} for the moments of inertia in atomic-weight-square-Ångström units of the same respective systems about an axis parallel to x through the centre of gravity of the alkyl halide, and I_y, I_{hy}, and I_{ay} for the corresponding moments of inertia about an axis parallel to y through the centre of gravity. When $\Delta_x = \Delta_y$, $I_x = I_y$, $I_{hx} = I_{hy}$, or $I_{ax} = I_{ay}$, we shall write Δ_{xy}, I_{xy}, I_{hxy}, or I_{axy} for either of the equal quantities. The frequencies, in cm.$^{-1}$, of the vibrations z_1, x_1, and y_1, denoted by ω_z, ω_x, and ω_y respectively, are given, for methyl and *tert.*-butyl halides, by the formulæ

$$4\pi^2c^2\omega^2_z = f_zMN/M_hM_a$$

$$4\pi^2c^2\omega^2_x = 4\pi^2c^2\omega^2_y = \Delta_{xy}I_{xy}N/10^{-16}I_{hxy}I_{axy}$$

and, for ethyl, *iso*propyl, *n*-propyl, *iso*butyl, and *neo*pentyl halides, they are given by the equations

$$4\pi^2c^2\omega^2_z = f_zMN/M_hM_a$$

$$4\pi^2c^2\omega^2_x = \Delta_xI_yN/10^{-16}I_{hy}I_{ay}$$

$$4\pi^2c^2\omega^2_y = \Delta_yI_xN/10^{-16}I_{hx}I_{ax}$$

Let us now extract, as we did from the formulæ for translational and rotational entropy, what the present formulæ for vibrational entropy teach of general principle concerning constitutional effects on entropy of activation. We shall find in vibrational entropy a more complicated situation than was encountered before, inasmuch as, now, both accelerating and retarding factors are present, which do not depend on steric hindrance, and also real steric effects, which themselves may be either accelerating or retarding.

The vibrational entropy of activation is given by the difference

$$S_v^{\ddagger} = S'_v(\mathrm{XRX}^-) - S_v(\mathrm{RX})$$

since $S_v(\mathrm{X}^-) = 0$. (The dash in the symbol for the transition-state term is added as a reminder that a transition state has one vibration less than it would have if it were a molecule.) The vibrational-entropy formula shows that vibrational entropies rise as frequencies fall. The frequency formulæ contain both masses and moments of inertia, always to a higher power in the denominator than in the numerator, and often in the form of a sum divided by the product of its parts. These formulæ therefore show that the general effect of an added mass, as on proceeding to a higher homologue, will be to lower frequencies and raise vibrational entropies, but to do these things less strongly in the transition state than in the initial state, because the mass and moments of inertia of the former are larger, and so the changes they suffer are proportionally smaller.* On this count, an added mass will reduce vibrational entropy of activation, and to that extent reaction rate. On the other hand, there are a larger number of frequencies to be lowered, and their entropy contributions raised, by an added mass in the transition state, than in the initial state. For this reason, an added mass could raise vibrational entropy of activation, and hence the

* The asymptotically logarithmic relation of frequency to entropy follows by expanding the summand of S_v in the series

$$R(-\ln x + 1 + x^2/24 + \text{higher-power terms})$$

which converges with increasing rapidity as $x = h\nu/kT$ becomes smaller.

frequency of reaction rate. Moreover, for reasons similar to those considered in connexion with rotational entropy, stronger rate-depressing effects on the first count, and stronger rate-enhancing effects on the second, may arise in the group of vibrations which depend on moments of inertia, when the extra mass is added nearer the reaction centre. Finally, our formulæ make some allowance for the circumstance that all parts of an alkyl group are not equally coupled to the motion of the halogens. The summing-up of this situation is involved in its detail, but it can be shown to yield the conclusion that, in a purely aliphatic system such as ours, an added mass will in general reduce the vibrational entropy of activation, but that a sufficient loading with extra masses near the reaction centre may increase it. Of course, neither the implied general retarding effect, nor the more specialised accelerating effect on the frequency factor of reaction rate, is of steric origin, since it would be the same if the added mass had no bulk. Indeed, if we were discussing isotopic substitution by a heavier isotope there would be nothing more to say.

But vibrational frequencies depend, not only on mass factors, but also on force-constants; and it is here that steric hindrance can come in quite genuinely, though not always with the effects we might have expected. It is sufficient to think now only of the transition state, in which the main steric pressures occur. The force-constants which control the vibrations of the reacting atoms in the transition state are determined by the narrowness and depth of the potential hollow, the bottom of which is occupied by the configuration of the transition state. The effect of steric pressure is to " push " this potential well either outwards or sideways, or in both ways; and, as to the influence of such displacements on the shape of the well, all will depend on whether it is displaced against a steepening energy cliff, or into a region of gentler energy gradients. If the displacement is outwards, and so into a region where a Morse curve would begin to curl over, the energy hollow will become shallower in that direction, as is already illustrated in Dostrovsky, Hughes, and Ingold's paper by their Fig. 6; and if such outward displacement were to relieve lateral steric pressure, then the hollow would become shallower laterally. In any case, increased proximity to the lip in the energy surface, which occurs further out than the transition state, will lead to smaller force-constants, lower frequencies, and more vibrational entropy in the transition state, and therefore to a higher vibrational entropy of activation, and to a steric enhancement of the frequency factor of reaction rate. But, to take another case, suppose that the steric displacement of the energy hollow is sideways, against the steepening wall of an essentially harmonic bending potential. Then the hollow will be narrowed, the force-constants and frequencies will be increased, and the vibrational entropy of activation will be reduced; so that, for this steric reason, the frequency factor of reaction rate will be diminished.

It seems correct to apply the term " non-steric " to that part of the effect of added masses which depends on their position but not on their volume, because the word " steric " implies a space-filling quality, and comes from a root meaning " solid." It may be convenient to have a collective (and positive) name for those non-polar, non-steric, entropy effects which depend on mass, including its position, but without bulk and without charge: such effects could be called " ponderal " entropy effects, since they follow from the mechanics of mass-points.* We can then distinguish three possible kinds of entropic effects of structure on reaction rate (and equally on reaction equilibria), *viz.*, ponderal, steric, and polar. (It is only because the present study of structural effects is restricted to alkyl groups that we shall have hardly any concern in this paper with polar entropic effects.)

In our numerical calculations of vibrational entropy, we met the difficulty, already encountered in the calculations of rotational entropy, that, in the cases of *n*-propyl and *iso*butyl halides, we do not know the proportions in which the conformations occur. Here, as before, we pursued the routine of calculating for all conformations, and accepting the average of the resulting entropies.

The numerical data used in the entropy calculations described, apart from those on which the energy surfaces are based, consist only of some vibration frequencies, as noted

* After consultation with the Editor, the established word " ponderal " (definition: pertaining to weight) has been adopted. Its meaning is clearly different from that of " ponderous " (definition: having great weight).

in Table 4. Those for the methyl halides are from the work of Bennett and Meyer, Barker and Plyler, and Noether, as collated by Herzberg (" Infra-red and Raman Spectra," van Nostrand, New York, 1945, p. 315), and those for the ethyl halides are values cited by Kohlrausch (" Der Smekal-Raman-Effekt," Springer, Berlin, 1938, Ergänzungsband, p. 133), as being derived from various consistent observations of Raman spectra; and they are among the values used by Cross and van Vleck (*loc. cit.*) for computing one of the types of force-constant which we have employed in the construction of our energy surfaces.

TABLE 4. *Adopted basic frequencies (in cm.*$^{-1}$).

RX	RCl	RBr	RI
MeX (CX-stretching)	732	611	533
MeX (HCX-bending)	1015	952	880
EtX (CCX-bending)	335	292	262

Our reactions occur in solution, and therefore one further type of contribution to the entropies of the initial and transition states must be considered, *viz.*, entropy of solvation. The entropy of solvation of the halide ion in the initial state will be a large negative quantity, because the central charge will cut away some translational and rotational entropy from the nearer solvent molecules; but it will always be the same, and will therefore appear only as part of an unevaluated constant term in the entropies of activation, and will disappear from their differences, which are all that we compare with experiment. Solvation being a local matter, we can consider the entropy of solvation of the transition state in two parts. By far the most important is the entropy of solvation of the pair of halogen atoms, each bearing half the total anionic charge, and we may, if we choose, take in the carbon atom between them. This entropy term will also be large and negative; but it too will be the same in all cases, and so will come into the constant term of the entropy of activation, and will disappear from the differences with which we are concerned. Similarly, we can divide the solvation entropies of the alkyl halide molecules into two parts, and consider first the part dependent on the dipolar CHal-group. This will be almost the same from case to case, and so will provide another, though relatively small, contribution to the constant term in the entropy of activation, and, once again, will disappear from the differences. There remain the solvation entropies of the rest of the alkyl group in the transition state, and of the rest of it in the initial state. These terms will be much smaller than any so far considered, but they will certainly change from case to case; however, the changes in the transition and initial states should be equivalent, and therefore the difference of the terms for the two states of any one alkyl group should remain constant when we change the alkyl group; and thus these terms, taken collectively, will contribute, once more, only to the constant term of the entropy of activation, and will disappear from the differences of concern to us.

In three places in this sub-section, we have developed parts of the theory of effects of substitution on the frequency factor of reaction rate, and so it seems useful to collect the conclusions, especially as we shall be able to illustrate most of them, both from our numerical calculations, and from our experimental results. First, as to the ponderal entropy effect, we have concluded that the introduction of a massive substituent anywhere into a reacting aliphatic molecule, as on passing to a higher homologue, should reduce the frequency factor, although a sufficient loading near the reaction centre will weaken this effect and might conceivably reverse it. Secondly, in so far as bulk is associated with the added mass, and if the substituent is sufficiently close to the reaction centre for the bulk to be effective, a steric entropy effect will arise, which may either increase or decrease the frequency factor of reaction rate; and the tendency will be towards an increase if the steric thrust on the attacking reagent is predominantly outwards, but towards a decrease if its main effect is to deflect the reagent sideways. These are further effects that the elementary idea of steric hindrance would not lead one to expect. Thirdly, we have in principle to envisage polar entropic effects of the substituent, which could conceivably change the shape of the transition-state energy surface, and also alter the entropy of some of the solvent molecules around it in a non-self-balancing way. However, such effects

may well prove to be unimportant in saturated aliphatic molecules without strongly polar substituents, and we certainly expect them to be negligible in simple alkyl groups.*

The results of our entropy calculations are given, and compared with the kinetic observations, in Section D.

(C) Observed Arrhenius Energies of Activation and their Comparison with Calculated Values.

(a) *Observed Arrhenius Energies of Activation of Seven Bimolecular Finkelstein Substitutions with Seven Alkyl Groups.*—Because of our ignorance of the heat-contents of the initial states, and still more of the transition states, of reactions, Arrhenius energies of activation, though they contain heat-content differences, and thereby lack theoretical simplicity, constitute as useful an experimental approach as any we may make to the problem of the structure-dependence of the energies of activation of reacting systems. We therefore begin this comparison of experimental with the calculated results by collecting in Table 5 the Arrhenius energies of activation obtained from the experimental kinetic studies recorded in the seven preceding papers. (Here, as elsewhere, *neo*Pe stands for *neo*pentyl.)

Table 5. *Observed Arrhenius energies of activation (E_A in kcal. mole^{-1}) of bimolecular Finkelstein substitutions in acetone.*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
(1) $Cl^- + RCl$	20·2	21·5	—	—	—	—	—
(2) $Cl^- + RBr$	15·7	17·6	18·6	21·0	17·8	18·3	21·7
(3) $Cl^- + RI$	16·0	17·2	17·6	—	17·4	17·8	22·0
(4) $Br^- + RBr$	15·8	17·5	19·7	21·8	17·5	18·9	22·0
(5) $Br^- + RI$	16·3	17·7	18·5	—	17·9	18·8	23·2
(6) $I^- + RBr$	16·3	18·9	20·5	22·0 *	19·0	19·9	24·2
(7) $I^- + RI$	—	17·4	19·4	21·4	—	—	22·2

* Potassium iodide had to be used in the experiments from which this figure is derived. All the other figures in the Table were obtained by the use of lithium salts.

Table 6. *Increments due to alkyl homology (ΔE_A in kcal. mole^{-1}) in observed Arrhenius energies of activation of Finkelstein substitutions in acetone.*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
(1) $Cl^- + RCl$	0·0	1·3	—	—	—	—	—
(2) $Cl^- + RBr$	„	1·9	2·9	5·3	2·1	2·6	6·0
(3) $Cl^- + RI$	„	1·2	1·6	—	1·4	1·8	6·0
(4) $Br^- + RBr$	„	1·7	3·9	6·0	1·7	3·1	6·2
(5) $Br^- + RI$	„	1·4	2·2	—	1·6	2·5	6·9
(6) $I^- + RBr$	„	2·6	4·2	6·9 *	2·7	3·6	7·9
(7) $I^- + RI$ †	„	1·7	3·7	5·7	—	—	6·5

* Since one of the two activation energies, of which this is a difference, had to be obtained by the use of potassium iodide, instead of lithium iodide (cf. note under Table 5), the activation energy subtracted from it, in order to give the figure here entered, is the methyl activation energy obtained comparably, not the value for methyl entered in Table 5.

† The figures in this row are based on an assumed E_A value of 15·7 kcal. mole^{-1} for the methyl group, a figure estimated by survey of the other methyl–ethyl differences, as well as such general differences as can be seen between the figures of one row and another. Therefore the ethyl figure in this row should be regarded as assumed.

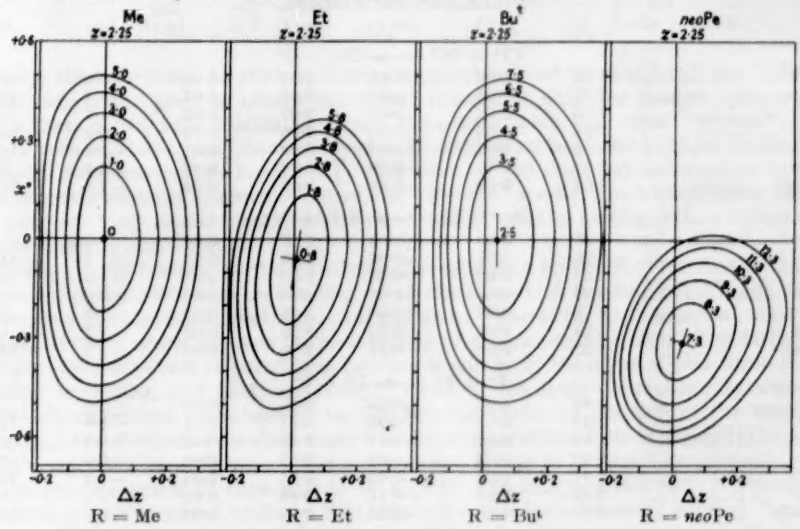
Our object is to consider the kinetic effect on these reactions of those structural changes which convert the methyl group into the higher alkyl groups. If there are either polar or steric effects, we can only define them relatively, and with reference to the methyl group as standard. Therefore, the experimental energy quantities that we shall seek to relate to theory are the excesses, for each Finkelstein substitution, of the Arrhenius energies of activation of the higher alkyl groups over that of the methyl group. These excesses are given, for ready reference, in Table 6.

One of the more general features of Table 6 is that, notwithstanding the scatter of the

* In Ivanoff and Magat's theory, the whole entropic effect of alkyl structure on reaction rate is described as steric (*J. Chim. phys.*, 1950, **47**, 914). This cannot be correct, as is implicit in the formulæ of Bauer and Magat (*ibid.*, p. 922). On the other hand, Ivanoff and Magat's treatment has the merit of being very simple.

figures in any one column, they exhibit no very marked general dependence on the nature of the involved halogens. Dostrovsky, Hughes, and Ingold predicted this theoretically (*loc. cit.*). That polar effects in the alkyl structures should not be much affected by the nature of the halogens is not surprising, because polar effects often conform to linear free-energy relations, and the polarities of halogen atoms are somewhat closely grouped. But that the steric effects, which are believed to be responsible for a large part of the differences of activation energy, should be insensitive to the sizes of the halogens, does at first sight seem surprising; and this conclusion was offered by the authors cited as an example of a prediction that the classical theory of steric hindrance could not have made, but which could be made on the basis of the reconstructed theory.

FIG. 3. *Calculated energy surfaces for the reactions* $Br^- + RBr \longrightarrow BrR + Br^-$. *The figures against the contours are energy co-ordinates in kcal. mole*$^{-1}$, *reckoned from the lowest point of the methyl surface as zero. For explanation of the spatial co-ordinates, see Fig.* 1. *The configurations which by calculation the transition states would have in the absence of steric hindrance are indicated by the intersections* (0,0) *of the co-ordinates shown, whilst their actual calculated configurations are marked* ●. *The relative heights of the surfaces control the calculated contribution of steric hindrance to the energy of activation, and their relative shapes its calculated contribution to the entropy of activation.*



A second general feature of Table 6 is that, in all reactions, the activation energies rise with homology, but in different ways in the α- and β-methylated series. Along the α-series, Me, Et, Pr^i, Bu^t, the rise can be described as roughly steady, if we make a generous allowance for the irregularities. Along the β-series, Et, Pr^n, Bu^i, *neo*Pe, the rise across the first interval is insignificant, across the second moderate, and across the third large. These are just the trends which Dostrovsky, Hughes, and Ingold deduced by their calculation, though the main experimental support they had at the time consisted of four activation energies, providing only two next-homologue differences, for the alkaline ethanolysis of the alkyl bromides.

There is one further, but less general, feature in Table 6, *viz.*, the tendency to high values in the reaction $I^- + RBr$. But the presumed cause of this is such that its discussion is more appropriately given in a paper, at present in draft, which belongs to another series.

Some of the so-called irregularities in Table 6 could probably be discussed in relation to constitution; but we make no such attempt, because of the difficulty of sorting them out unambiguously from the real irregularities, due to disregarded heat-content terms, and to observational error.

(b) *Calculated Configurations of Transition States and Calculated Steric Contributions to Activation Energy for Three Symmetrical Finkelstein Substitutions with Seven Alkyl Groups.*—The method of these calculations is described in Section B: for each type of halogen, and each alkyl group, we have first to construct a surface representing energy as a function of the configuration of the reacting system. Each such surface contains a hollow, the bottom of which represents the transition state. Contour diagrams of some of the calculated energy surfaces are shown in Fig. 3.

We deal in this Section only with the positions of the minima, and first with their spatial co-ordinates. As Fig. 3 illustrates in three examples, all alkyl groups, above methyl, displace the minima, that is, the positions of the halogen atoms in the transition states, outwards from the α-carbon atom by some hundredths of an Å. Furthermore, all these groups, with the one exception of the *tert.*-butyl group, displace the minimum sideways by some 5—10 times as much. The spatial co-ordinates of the minima of all the surfaces calculated are given in Table 7. Here Δ_z represents the outward displacement of the halogen atoms

TABLE 7. *Calculated spatial co-ordinates of the transition states in bimolecular Finkelstein substitutions.*

R	z (Å)	Δz (Å)	x° (Å)	r (Å)	Δr (Å)	θ	
		$Cl^- + RCl \longrightarrow ClR + Cl^-$					
Me	2·05	0·00	±0·00	2·05	0·00	±0·0°	—
Et	2·06	0·01	−0·05	2·06	0·01	−1·4	11°
Pr^i	2·07	0·02	+0·06	2·07	0·02	+1·7	—
Bu^t	2·08	0·03	±0·00	2·08	0·03	±0·0	—
Pr^n	2·06	0·01	−0·05	2·06	0·01	−1·4	11
Bu^i	2·07	0·02	−0·08	2·07	0·02	−2·2	0
*neo*Pe	2·07	0·02	−0·27	2·09	0·04	−7·4	21
		$Br^- + RBr \longrightarrow BrR + Br^-$					
Me	2·25	0·00	±0·00	2·25	0·00	±0·0°	—
Et	2·26	0·01	−0·06	2·26	0·01	−1·5	11°
Pr^i	2·27	0·02	+0·08	2·27	0·02	+2·0	—
Bu^t	2·29	0·04	±0·00	2·29	0·04	±0·0	—
Pr^n	2·26	0·01	−0·06	2·26	0·01	−1·5	11
Bu^i	2·28	0·03	−0·09	2·28	0·03	−2·3	0
*neo*Pe	2·28	0·03	−0·31	2·30	0·05	−7·7	21
		$I^- + RI \longrightarrow IR + I^-$					
Me	2·46	0·00	±0·00	2·46	0·00	±0·0°	—
Et	2·47	0·01	−0·08	2·47	0·01	−1·9	11°
Pr^i	2·48	0·02	+0·11	2·48	0·02	+2·5	—
Bu^t	2·50	0·04	±0·00	2·50	0·04	±0·0	—
Pr^n	2·47	0·01	−0·08	2·47	0·01	−1·9	11
Bu^i	2·49	0·03	−0·11	2·49	0·03	−2·5	0
*neo*Pe	2·50	0·04	−0·39	2·53	0·07	−8·8	22

in the transition state, and x° their lateral displacement; whilst Δ_r is the increase in the length of a halogen semi-bond, 2θ the angle by which the split XRX-bond is bent, and ϕ' is the angle through which the plane of bending is twisted relatively to the stem from C_α of the group responsible for the bending. One sees that by far the largest deformations of the split bond are those produced by the *neo*pentyl group, which, in the iodine reaction, lengthens it by 0·14 Å, bends it by 17·6°, and twists the plane of bending away from the stem of the group by 21°. All this has a great effect on the energy at the minimum.

We now turn to the energy co-ordinates. The energy of steric hindrance (or, of steric retardation, since a kinetic, not a thermodynamic, problem is under discussion), due to any group R, is in principle defined as a second difference:

$$W_S(R) = \left(W_R^{\text{transition}} - W_{Me}^{\text{transition}}\right) - \left(W_R^{\text{initial}} - W_{Me}^{\text{initial}}\right)$$

But in calculations by our method, in the cases we have studied, the second term in parentheses, if not zero, is always negligible. Left with the first main term, we set the zero of energy at $W_{Me}^{\text{transition}}$, and thus introduce the convenient approximate definition,

$$W_S(R) = W_R^{\text{transition}}$$

That is, the energies of steric retardation of our reactions can with sufficient accuracy be identified with the energy co-ordinates of the minima of the calculated reaction surfaces.

These co-ordinates are in Table 8, in compiling which the opportunity has been taken to illustrate the effects of the successive relaxations that have been allowed to modify the model originally used by Dostrovsky, Hughes, and Ingold. This " stiff " model, yielded an energy curve and did not allow its shape to change : energies thus calculated by them or by ourselves, are headed W_s^{st} in Table 8. In a few cases, the previous authors tried

TABLE 8. *Calculated energies of steric retardation in bimolecular Finkelstein substitutions (kcal. mole^{-1}).*

	$Cl^- + RCl \rightarrow ClR + Cl^-$			$Br^- + RBr \rightarrow BrR + Br^-$			$I^- + RI \rightarrow IR + I^-$		
R	W_s^{st}	W_s^{el}	W_s^{pl}	W_s^{st}	W_s^{el}	W_s^{pl}	W_s^{st}	W_s^{el}	W_s^{pl}
Me	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Et	1·1	—	0·8	0·9	—	0·8	0·8	—	0·7
Pr^i	2·2	2·0	1·6	1·9	1·8	1·6	1·4	1·4	1·3
Bu^t	3·2	2·8	2·8	2·8	2·5	2·5	2·2	2·0	2·0
Pr^n	1·1	—	0·8	0·9	—	0·8	0·8	—	0·7
Bu^i	2·5	—	2·1	2·8	—	2·3	3·2	—	2·5
*neo*Pe	11·5	10·8	6·5	13·9	12·9	7·3	~20	~18	7·8

allowing the semi-bonds to stretch, thereby employing what we might call the " elastic " model, which also gave an energy curve, but allowed its shape to change : the energies which they, or we, have calculated on this basis are headed W_s^{el}. Our " plastic " model allows both stretching and bending, yields an energy surface, and permits its shape to change : these energies are headed W_s^{pl}. We have not yet done any calculations with the other possible model of intermediate type, the " flexible " model, which would allow bending but not stretching ; but it would probably be a useful model for getting certain approximate results with the least labour.

Three general features of these theoretical results may be noted. The first is that the relaxation of the restriction on bending, in all cases in which bending could occur, lowers appreciably the calculated steric energies, and greatly lowers the high energies. The most striking of these effects are seen in the reactions of the *neo*pentyl group. The early guess that the energetic effect of permitting bending would be of the order of four times that of allowing stretching, and that, accordingly, much of the large discrepancy between the previously calculated steric energy for the bromine-exchange reaction of the *neo*pentyl group, and the observed activation energy of the alkaline ethanolysis of *neo*pentyl bromide, would disappear if bending were taken into account, is seen to be broadly confirmed.

The reasonableness of expecting to be able thus to compare two such different substitutions as the bromine exchange and alkaline ethanolysis involved another " guess," which was that energies of steric retardation in bimolecular nucleophilic substitution in saturated systems would be found to be only mildly dependent on the sizes of the entering and displaced groups. In Table 8, we see that the steric energies, calculated with the " plastic " model, for the iodine-exchange reaction, never differ very much from those similarly computed for the chlorine-exchange reaction ; and, moreover, that the energies of the iodine reaction are not only sometimes greater, but are also sometimes less, than the energies of the chlorine reaction. The reason for the two directions which this difference may take is that the increased outward pressure which acts on the larger halogen adds its potential to others, including that of a Morse curve which has been displaced outwards, and hence provides less energy in the relevant region, whereas the increased lateral pressure adds its potential to others, including that of an undisplaced harmonic curve.

Finally, with regard to the effect of alkyl structure on steric energy, the new calculations confirm the old qualitatively, though not quantitatively. We find the same sharp distinction between the α- and β-methylated series. In the α-series, Me, Et, Pr^i, Bu^t, the steric energy rises, not regularly in principle as before (for it is an artefact of the " stiff " model that α-substituents act independently), but still, very nearly regularly. On the other hand, along the β-series, Et, Pr^n, Bu^i, *neo*Pe, the successive energy steps steepen markedly, even

though less sharply than before; for it remains true that the first step is zero, whilst the third is by much the largest of any shown by a pair of neighbouring homologues.

(c) *Comparison of Differences of Experimental Arrhenius Energies of Activation with Calculated Steric Contributions to Energies of Activation.*—For bimolecular reactions of ideal solutes in solution, the Arrhenius energy of activation E_A is related to the heat of activation $H^\ddagger$ by the equation, $E_A = H^\ddagger + \boldsymbol{R}T$, so that, for a standard temperature, we can equate corresponding differences in each quantity, and, in particular, write :

$$\Delta E_A = E_A(\mathrm{R}) - E_A(\mathrm{Me}) = H^\ddagger(\mathrm{R}) - H^\ddagger(\mathrm{Me}) = \Delta H^\ddagger$$

We have been measuring the former difference experimentally, and, of the latter, we have been computing the steric portion,

$$\Delta W_S = W_S(\mathrm{R}) - W_S(\mathrm{Me}) = W_S(\mathrm{R})$$

since the methyl group provides our zero. In general, we must expect that other properties of substituents, chemically more specific than their geometry, properties which we summarise as polar, will also contribute to $H^\ddagger$, and thus to E_A; and the structural differential of such contributions may be defined as the polar portion of ΔH and of ΔE_A, as follows :

$$\Delta W_P = W_P(\mathrm{R}) - W_P(\mathrm{Me}) = W_P(\mathrm{R}),$$

the methyl group again providing the zero. This definition leads to the simple summation,

$$\Delta E_A = \Delta W_S + \Delta W_P$$

We do not yet know a feasible method of computing the polar contribution ΔW_P without the use of adjustable constants, and so it is of interest to compare experimental values of ΔE_A with calculated values of ΔW_S, and note what the differences suggest as to the values which ΔW_P may have, and as to how these values vary with structure.

Dostrovsky, Hughes, and Ingold noticed that, except that the *neo*pentyl group was out of line, for reasons which they thought they understood, their calculated steric energies fell below the relevant differences of experimental activation energy, by amounts which seemed to increase with α-branching. They ascribed the differences to the polar influence on the reaction of α-methyl groups, assuming that β-methyl groups would have relatively very small polar effects at the reaction centre. The conclusion that such polar effects are involved in bimolecular nucleophilic substitution has since been contested by A. G. Evans (*loc. cit.*; *Nature*, **1946**, **157**, 438; **158**, 586; **1947**, **159**, 166; *Trans. Faraday Soc.*, **1946**, **42**, 719; Evans, Evans, and Polanyi, *J.*, **1947**, 558; cf., however, Hughes and Ingold, *Trans. Faraday Soc.*, **1947**, **43**, 798, and Dostrovsky, Hughes, and Ingold, *J.*, **1948**, 1283), but, in view of the discussion in Section A of this paper, and the further theoretical and experimental examination of the problem summarised in Sections B and C, it seems to be a difficult conclusion to avoid, even on physicochemical grounds, supposing that one remained unimpressed by the extensive organic-chemical evidence in favour of polar effects on such reactions.*

For simplicity of illustration, we shall make the approximation of assuming that the

* In the first of the papers cited, Evans reported a theoretical study of Finkelstein iodine-exchange for the *tert.*-butyl group with reference to its calculated steric energy, which, he believed, would account for the whole of the experimental excess of the activation energy of this reaction over that of the corresponding reaction of the methyl group. His calculated steric energy, 2 kcal. mole^{-1}, agrees, despite differences of method (cf. Section A), with our calculated value 2·0 kcal. mole^{-1} (Table 8). Evans's only comment on his value was that the experimental excess of activation energy was (in **1947**) unknown. However, there was at that time a clear indication in the work of le Roux, Lu, Sugden, and Thompson (*J.*, 1945, 586) on Finkelstein bromine-exchange for *n*- and *tert.*-butyl in ethylene diacetate, that the excess of energy from methyl to *tert.*-butyl for that reaction would be at least 5 kcal. mole^{-1}. It has now been found to be 6·0 kcal. mole^{-1} in acetone, the corresponding value for the iodine-exchange being close to 6·5 kcal. mole^{-1} (cf. Tables 5 and 6). It is therefore not obvious how Evans reached his conclusion that nothing beyond steric hindrance was required to account for differences in energy of activation in the bimolecular reactions of alkyl halides.

polar effects ΔW_P of α-methyl substituents on the activation energies of our reactions may be taken as independent, and that those of the β-substituents may be neglected. Then it is found that the single rounded value 1 kcal. mole^{-1}, for the polar effect ΔW_P of an α-alkyl substituent, brings all the computed totals into approximate agreement with the experimental differences of activation energy ΔE_A, except for one discrepancy of a not unreasonable magnitude just where we might expect it. Two illustrations of this are given in Table 9. First, the comparison is made for an individual Finkelstein substitution : we choose bromine-exchange, because it is one of the reactions for which calculations have been completed, and, on the experimental side, it is one of the most satisfactorily studied. The necessary figures are taken from Tables 6 and 8 (W_g^1 values from the latter). Then because the nature of the halogen makes so little systematic difference to either calculated or experimental figures, we average, for each alkyl group, all the available figures in Table 6, and all those (W_g^1 values) in Table 8, and make the comparison with the averages. In each illustration, the only notable discrepancy is with the *neo*pentyl group, where the calculated compression energies are so large, that the prohibition, by even the " plastic " model, of alkyl deformation will constitute an approximation, the effect which we would expect to notice in our results.

TABLE 9. *Comparison of calculated and observed effects of alkyl structure on energies of activation (kcal. mole^{-1}).*

	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
	Reaction : $Br^- + RBr \longrightarrow BrR + Br^-$						
ΔW_S	0	0·8	1·6	2·5	0·8	2·3	7·3
ΔW_P	0	1	2	3	1	1	1
ΔE_A (calc.)	0	1·8	3·6	5·5	1·8	3·3	8·3
ΔE_A (obs.)	0	1·7	3·9	6·0	1·7	3·1	6·2
Difference	0	+0·1	−0·3	−0·5	+0·1	+0·2	+2·1
	Averages for all investigated reactions.						
ΔW_S	0	0·8	1·5	2·4	0·8	2·3	7·2
ΔW_P	0	1	2	3	1	1	1
ΔE (calc.)	0	1·8	3·5	5·4	1·8	3·3	8·2
ΔE (obs.)	0	1·7	3·1	6·0	1·9	2·7	6·6
Difference	0	+0·1	+0·4	−0·6	−0·1	+0·6	+1·6

The retarding polar effect, to which our results point, evidently belongs to the class of polar effect on bimolecular substitutions in alkyl compounds, which was identified with the positive inductive effect (+*I*) in some of the earliest papers on nucleophilic substitution (Hughes, Ingold, and Patel, *J.*, 1933, 526; Gleave, Hughes, and Ingold, *J.*, 1935, 236; Hughes and Ingold, *J.*, 1935, 244). This identification assumes that, in simple alkyl halides, the bound halogen atom is so unready to separate as a halide ion that in bimolecular substitution the anionic reagent has to press its attack extensively before a transition state is formed, at which point the two potential anions together will not carry quite the whole of the anionic charge, but will force some of it on to the α-carbon atom. But, as was emphasized in the same period (Hughes, Ingold, and Shapiro, *J.*, 1936, 225), though the point is disregarded in the subsequent arguments of A. G. Evans (*locc. cit.*), the conditions may well be different in bimolecular substitutions of unsaturated halides rendered intrinsically ionisable by an electromeric effect. For then, a considerably less far-pressed attack by an anion may produce a bimolecular transition state in which a total of rather more than a unit of negative charge is claimed by the two would-be anions, leaving a small positive charge on the α-carbon atom, with the result that the positive inductive effect is accelerating.* This overall duplexity of direction in polar effects in bimolecular substitution, in contrast to their uniformity in unimolecular substitution, has often been noted since.

* Hughes, Ingold, and Shapiro took the benzyl system as their example, as this point was demonstrable from the work of Baker and Nathan (*J.*, 1935, 1844). Catchpole and Hughes later showed that the allyl system behaved similarly (*Trans. Faraday Soc.*, 1941, **37**, 207; cf. Vernon, *J.*, 1954, 4462). Without reference to Hughes, Ingold, and Shapiro's discussion of the benzyl case, Evans cites differences between effects of methyl substitution in simple alkyl and in allyl systems as an inconsistency; but it would have been reasonable to assume that the earlier discussion of benzyl would be applicable to allyl.

Other ways of inducing a change of direction of the kinetic polar effect in bimolecular substitution are known, and yet others can be foreseen, but have still to be realised.

(D) Observed Arrhenius Frequency Factors and their Comparison with Calculated Values.

(a) *Observed Arrhenius Frequency Factors for Seven Bimolecular Finkelstein Substitutions with Seven Alkyl Groups.*—Although the Arrhenius frequency factor B, like the energy of activation E_A, involves heat-capacity terms, it constitutes as good an experimental approach as any available to the problem of the structure-dependence of the entropy changes which accompany activation in reactions. We therefore collect in logarithmic form, in Table 10, the Arrhenius frequency factors, which have been derived from the observations recorded in the seven preceding papers. It should be noted that these values will to some extent be dependent on the salt conditions applying to the measurements. These were approximately standardised along any horizontal row of the Table, but could not be standardised from row to row because different salts are involved. The approximate salt conditions applying to the different rows are as follows: (1) 0·027M-LiCl; (2) 0·07M-LiCl; (3) 0·10M-$LiClO_4$ + 0·03M-LiCl; (4) 0·024M-LiBr; (5) and (6) 0·024M-LiI; (7) 0·09M-LiI. The negative salt effects of the different salts are probably in the order $LiClO_4 > LiI > LiBr > LiCl$, and increase, at first markedly, and later more mildly, with increasing salt concentration. If we could bring all the values in the Table to a common salt standard, say that of row (1), the greatest positive correction to $\log_{10} B$, perhaps 0·5 unit, would be required in row (3), and the other corrections would be smaller in the order

$$(3) > (7) > \underbrace{(5) \text{ and } (6)}_{(2)} > (4) > (1) = \text{zero}$$

Although we have more extensive information on the salt effect than appears in these papers, we still have not enough to make these corrections quantitatively, and so we do not attempt them.

Table 10. *Logarithms of observed Arrhenius frequency factors* ($\log_{10} B$, *with* B *in sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *of bimolecular Finkelstein substitutions in acetone.*

R	Me	Et	Pr^i	Bu^s	Pr^n	Bu^i	*neo*Pe
(1) Cl^- + RCl	10·3	9·5	—	—	—	—	—
(2) Cl^- + RBr	9·3	8·9	7·9	8·9	8·6	8·4	7·4
(3) Cl^- + RI	9·4	9·1	8·3	—	8·8	8·3	7·9
(4) Br^- + RBr	10·7	10·1	9·7	10·7	9·8	9·6	8·6
(5) Br^- + RI	11·4	11·1	10·2	—	10·8	10·3	10·1
(6) I^- + RBr	11·4	11·0	10·2	10·2 *	10·8	10·3	10·2
(7) I^- + RI	—	11·5	11·0	12·0	—	—	10·2

* See note under Table 5.

Though there are some exceptions, one cannot but notice the general trend towards higher frequency factors, for any one alkyl group, as the atomic number of either halogen is increased, and the near-constancy of the values as between the two reactions, (5) and (6), which use the same pair of halogens with reversed functions. We are not able to offer any very useful discussion of this, because the comparisons involve, not merely the effect of structural changes on the behaviour of a given set of reacting atoms, but also changes in the reacting atoms; with the consequence that the unevaluated terms in our calculated energies and entropies of activation, such as, for example, the solvation entropy of the charged species, are not self-balancing.

When we pass from the frequency factors themselves to the ratios in which they are changed by modifications of the alkyl group, then the problem of interpretation falls much more nearly within our capacity. As our object is to study the kinetic effects of those structural changes which convert the methyl group into higher alkyl groups, we assemble in Table 11 the excesses of the logarithms of the frequency factors for the higher alkyl groups over those for the methyl group.

In these figures we find no general trend, when, for any one alkyl group, the halogens

are changed. Instead, we see irregularities so unsystematic as to make one feel that an average is worth almost as much attention as any individual value.

On the other hand, the differences from one alkyl group to another show consistent common features. Along the α-series, Me, Et, Pr^{i}, Bu^{s}, the differences at first fall, in two considerable steps as far as Pr^{i}; and then for Bu^{s} the values show a sharp rise. This is in

TABLE 11. *Observed increments, due to alkyl homology, in the logarithms of the Arrhenius frequency factors* ($\Delta\log_{10} B$, *with B in sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *of Finkelstein substitutions in acetone.*

R:	Me	Et	Pr^{i}	Bu^{s}	Pr^{n}	Bu^{i}	*neo*Pe
(1) Cl^- + RCl	0·0	−0·8	—	—	—	—	—
(2) Cl^- + RBr	,,	−0·4	−1·4	−0·4	−0·7	−0·9	−1·9
(3) Cl^- + RI	,,	−0·3	−1·1	—	−0·6	−1·1	−1·5
(4) Br^- + RBr	,,	−0·6	−1·0	±0·0	−0·9	−1·1	−2·1
(5) Br^- + RI	,,	−0·3	−1·2	—	−0·6	−1·1	−1·3
(6) I^- + RBr	,,	−0·4	−1·2	−0·3 *	−0·6	−1·1	−1·2
(7) I^- + RI †	,,	−0·5	−1·0	±0·0	—	—	−1·8

* See notes under Tables 5 and 6; the figure here entered is the difference of values obtained for the *tert.*-butyl and the methyl group in comparable experimental conditions, with potassium iodide as reagent.

† The figures in this row are based on an assumed $\log_{10} B$ value of 12·0 for the methyl group, a figure estimated by survey of the other methyl–ethyl differences. Therefore the ethyl value in this row is to be regarded as assumed.

marked contrast to the energy variation, which we saw to be almost linear throughout the α-series. In the β-series, Et, Pr^{n}, Bu^{i}, *neo*Pe, the logarithmic differences of frequency fall in substantial steps throughout. The contrast here with the energy variation is that the steps do not progressively steepen throughout the series in the same marked way.

(b) *Calculated Effects of Alkyl Structure on the Entropies of Activation of the Finkelstein Substitution of Bromine Exchange.*—Our programme is to make such calculations for all the Finkelstein substitutions for which we have the energy surfaces; but, whereas our calculations on the bromine exchange reaction are complete, those on other substitutions are not, and are proceeding somewhat slowly. Therefore we have decided to report what is finished, rather than to delay further the publication of our work of the last 9 years.

The method of calculation is described in Section C. In summary, we compute translational, rotational, and vibrational entropies for the initial alkyl halide, and for the transition state. We do not trouble about those entropy terms which are self-balancing in the differences of activation entropy, *viz.*, the translational entropy of the halide ion, and the solvation entropies. Each vibrational entropy is the sum of terms corresponding to the normal vibrations; however, our model, which assumes pliability around the reaction centre, but stiffness in the remainder of the alkyl group, allows us to neglect intra-alkyl vibrations, but requires us to calculate the other vibrational terms with what their frequencies would be if the alkyl groups were stiff. For transition states, the rotational entropies depend on the spatial co-ordinates of the minima of the energy surfaces of the reactions, whilst the vibrational entropies depend on the curvatures of the surfaces around the minima. For the normal states of the *n*-propyl and *iso*butyl groups, we calculate for all conformations, weighting the results equally in the final averages. The detailed results for the calculated parts of the entropies of the transition and initial states are given in Table 12. The notation is explained in Section C, but Figs. 1 and 2 will be a sufficient reminder. A brace indicates vibrations of the same symmetry species, whose entropy contributions, if different, are indeterminately interchangeable.

The effects of structure on the components of the entropy of activation are to be calculated as second differences from the data of Table 12. It is instructive to proceed towards the second differences in both the possible ways, in order to be able to follow structural changes on the entropy of each state, as well as in the activation entropy:

$$S_R^{\ddagger} = S_R^{\text{transition}} - S_R^{\text{initial}}$$

$$\Delta S^{\text{transition}} = S_R^{\text{transition}} - S_{Me}^{\text{transition}}; \quad \Delta S^{\text{initial}} = S_R^{\text{initial}} - S_{Me}^{\text{initial}}$$

$$\Delta S^{\ddagger} = S_R^{\ddagger} - S_{Me}^{\ddagger} = \Delta S^{\text{transition}} - \Delta S^{\text{initial}}$$

The two sets of first differences, and the second differences, are given, in partly summarised form, in Table 13.

The translational entropy of the bromide ion is 13·58 cal. deg.$^{-1}$ mole^{-1}. This should be added to all initial-state entropies, and subtracted from all entropies of activation. It disappears from the second differences. The solvation entropies are unevaluated, and they too should disappear from the second differences.

These figures illustrate a number of the rules, which in Section B were derived from theory, concerning both ponderal and steric effects of homology on entropy of activation, and thus on the frequency factor of reaction rate. The first is that the ponderal effect of mass apart from its position on the translational entropy produces a decrease in the translational entropy of activation as the molecular weight increases, as is illustrated by the following figures (cal. deg.$^{-1}$ mole^{-1}):

Me, 1·82; Et, 1·64; Pr^{n} and Pr^{i}, 1·49; Bu^{i} and Bu^{t}, 1·36; *neo*Pe, 1·26.

The second effect, essentially ponderal, though it involves both mass and position, is that rotational entropy of activation decreases as new masses are added, and does so the

TABLE 12. *Calculated translational, rotational, and vibrational entropies (in cal. deg.$^{-1}$ mole^{-1}), and their totals, for transition states and initial molecules in the bimolecular substitution,* $Br^- + RBr \longrightarrow BrR + Br^-$.

	Transition state.			*Initial state.*		
			R = *Methyl*			
S_t	$(\frac{3}{2})R \ln M$	15·39		$(\frac{3}{2})R \ln M$	13·57	
,,	Constants	0·52		Constants	0·52	
,,	Total		15·91	Total		14·09
S'	$(\frac{1}{2})R \ln ABC$	14·60		$(\frac{1}{2})R \ln ABC$	8·98	
,,	$-R \ln \sigma$	−3·56		$-R \ln \sigma$	−2·18	
,,	Constants	−3·69		Constants	−3·69	
,,	Total		7·35	Total		3·11
S_v	z_t	3·12		z_1	0·43	
,,	x_t	2·24		x_1	0·11	
,,	y_t	2·24		y_1	0·11	
,,	x_a	0·06		Total		0·65
,,	y_a	0·06				
,,	Total		7·72			
S			30·98			17·85
			R = *Ethyl*			
S_t	$(\frac{3}{2})R \ln M$	15·62		$(\frac{3}{2})R \ln M$	13·98	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·14	Total		14·50
S_r	$(\frac{1}{2})R \ln ABC$	17·10		$(\frac{1}{2})R \ln ABC$	12·55	
,,	$-R \ln \sigma$	−1·38		$-R \ln \sigma$	0·00	
,,	Constants	−3·69		Constants	−3·69	
,,	Total		12·03	Total		8·86
S_v	z_t	2·85		z_1	0·76	
,,	x_t	2·44		x_1	1·48	
,,	y_t	2·19		y_1	0·59	
,,	x_a	1·50		Total		2·83
,,	y_a	0·06				
,,	Total		9·04			
S			37·21			26·19

TABLE 12. (*Continued.*)

	Transition state.			*Initial state.*		
			R = iso*Propyl*			
S_t	$(\frac{3}{2})R \ln M$	15·83		$(\frac{3}{2})R \ln M$	14·34	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·35	Total		14·86
S_r	$(\frac{1}{2})R \ln ABC$	17·85		$(\frac{1}{2})R \ln ABC$	14·58	
,,	$-R \ln \sigma$	−1·38		$-R \ln \sigma$	0·00	
,,	Constants	−3·69		Constants	−3·69	
,,	Total		12·78	Total		10·89
S_v	z_t *	2·65		z_1	0·94	
,,	x_t *	2·65		x_1	1·04	
,,	y_t	2·13		y_1	2·13	
,,	x_a	0·92		Total		4·11
,,	y_a	1·69				
,,	Total		10·04			
S			39·17			29·86
			R = tert.-*Butyl*			
S_t	$(\frac{3}{2})R \ln M$	16·03		$(\frac{3}{2})R \ln M$	14·67	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·55	Total		15·19
S_r	$(\frac{1}{2})R \ln ABC$	18·30		$(\frac{1}{2})R \ln ABC$	15·60	
,,	$-R \ln \sigma$	−3·56		$-R \ln \sigma$	−2·18	
,,	Constants	−3·69		Constants	−3·69	
,,	Total		11·05	Total		9·73
S_v	z_t	3·46		z_1	1·09	
,,	x_t	3·41		x_1	2·14	
,,	y_t	3·41		y_1	2·14	
,,	x_a	2·21		Total		5·37
,,	y_a	2·21				
,,	Total		14·70			
S			42·30			30·29
			R = n-*Propyl*			
S_t	$(\frac{3}{2})R \ln M$	15·83		$(\frac{3}{2})R \ln M$	14·34	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·35	Total		14·86
S_r	$(\frac{1}{2})R \ln ABC$	18·30		$(\frac{1}{2})R \ln ABC$:		
,,	$-R \ln \sigma$	−1·38		*anti*	14·34	
,,	Constants	−3·69		each *syn*	14·63	
,,	Total		13·27	Average		14·53
,,				$-R \ln \sigma$		0·00
,,				Constants		−3·69
,,				Total		10·84
S_v	z_t	3·01		z_1		0·96
,,	x_t	2·58		x_1 : *anti*	2·32	
,,	y_t	2·19		each *syn*	2·11	
,,	x_a	2·15		Average		2·18
,,	y_a	0·06		y_1 : *anti*	1·28	
,,	Total		9·99	each *syn*	0·79	
,,				Average		0·95
,,				Total		4·09
S			39·61			29·79

TABLE 12. (*Continued.*)

		Transition state.		*Initial state.*		
		R = iso*Butyl*				
S_t	$(\frac{3}{2})R \ln M$	16·03		$(\frac{3}{2})R \ln M$	14·67	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·55	Total		15·19
S_r	$(\frac{1}{2})R \ln ABC$	18·85		$(\frac{1}{2})R \ln ABC$:		
,,	$-R \ln \sigma$	−1·38		*anti*	15·70	
,,	Constants	−3·69		each *syn*	15·85	
,,	Total		13·78	Average		15·80
,,				$-R \ln \sigma$		0·00
,,				Constants		−3·69
,,				Total		12·11
S_v	z_t	3·06		z_1		1·09
,,	x_t	2·54		x_1: *anti*	2·28	
,,	y_t	2·19		each *syn*	2·54	
,,	x_a	2·35		Average		2·45
,,	y_a	0·06		y_1: *anti*	1·05	
,,	Total		10·20	each *syn*	1·40	
,,				Average		1·28
,,				Total		4·82
S			40·53			32·12
		R = neo*Pentyl*				
S_t	$(\frac{3}{2})R \ln M$	16·22		$(\frac{3}{2})R \ln M$	14·96	
,,	Constants	0·52		Constants	0·52	
,,	Total		16·74	Total		15·48
S_r	$(\frac{1}{2})R \ln ABC$	19·37		$(\frac{1}{2})R \ln ABC$	16·68	
,,	$-R \ln \sigma$	−1·38		$-R \ln \sigma$	0·00	
,,	Constants	−3·69		Constants	−3·69	
,,	Total		14·30	Total		12·99
S_v	z_t	2·84		z_1	1·18	
	x_t	2·62		x_1	2·70	
,,	y_t	2·19		y_1	1·50	
,,	x_a	1·98				
,,	y_a	0·06		Total		5·38
,,	Total		9·69			
S			40·73			33·85

Note: The frequencies of the two vibrations marked with an asterisk are not identical in principle, but, as calculated, they were complex, differing only by an imaginary part, which was neglected. Their values were $(10^{13}/2\pi)\ (8{\cdot}29 \pm 0{\cdot}52i)^{\frac{1}{2}}$ sec.$^{-1}$. They were the only calculated frequencies to emerge in complex form.

more markedly the nearer the added masses are to the reaction centre. The following figures illustrate these effects of homology and of position-isomerism (cal. deg.$^{-1}$ mole^{-1}):

Me, 4·24; Et, 3·17; Pr^n, 2·62; Pr^i, 2·47; Bu^i, 1·67; Bu^t, 1·32; *neo*Pe, 1·31.

The comparison of Bu^t with *neo*Pe shows that the effect of shifting two methyl groups from the α- to the β-position almost cancels that of adding a third methyl group. Conformational isomerism does not follow such simple rules, for the reason that when we transfer two main masses, relatively to two between them, from *anti*- to *syn*-positions, the displacement brings them closer longitudinally, but also has a transverse component which moves them further off what was before the main line or plane of masses. We can see this conflict

TABLE 13. *Calculated effects of alkyl structure on entropies of transition and initial states, and on activation entropies (all in cal. deg.$^{-1}$ mole^{-1}) for bimolecular reactions :*

$$Br^- + RBr \longrightarrow BrR + Br^-.$$

	$S_R^{transition}$	$S_R^{initial}$	$S_R^{\ddagger}$	Differences from methyl: $\Delta S^{transition}$	$\Delta S^{initial}$	$\Delta S^{\ddagger}$
			Methyl			
Transl.	15·91	14·09	1·82	0·00	0·00	0·00
Rotn.	7·35	3·11	4·24	"	"	"
Vibrn.	7·72	0·65	7·07	"	"	"
Total	30·98	17·85	13·13	"	"	"
			Ethyl			
Transl.	16·14	14·50	1·64	0·23	0·41	−0·18
Rotn.	12·03	8·86	3·17	4·68	5·75	−1·07
Vibrn.	9·04	2·83	6·21	1·32	2·18	−0·86
Total	37·21	26·19	11·02	6·23	8·34	−2·11
			iso*Propyl*			
Transl.	16·35	14·86	1·49	0·44	0·77	−0·33
Rotn.	12·78	10·89	1·89	5·43	7·78	−2·35
Vibrn.	10·04	4·11	5·93	2·32	3·46	−1·14
Total	39·17	29·86	9·31	8·19	12·01	−3·82
			tert.-*Butyl*			
Transl.	16·55	15·19	1·36	0·64	1·10	−0·46
Rotn.	11·05	9·73	1·32	3·70	6·62	−2·92
Vibrn.	14·70	5·37	9·33	6·98	4·72	+2·26
Total	42·30	30·29	12·01	11·32	12·44	−1·12
			n-*Propyl* (anti-*conformation*)			
Transl.	16·35	14·86	1·49	0·44	0·77	−0·33
Rotn.	13·27	10·65	2·62	5·92	7·54	−1·62
Vibrn.	9·99	4·56	5·43	2·27	3·91	−1·64
Total	39·61	30·07	9·54	8·63	12·22	−3·59
			n-*Propyl* (*D*- or *L*-syn-*conformation*)			
Transl.	16·35	14·86	1·49	0·44	0·77	−0·33
Rotn.	13·27	10·94	2·33	5·92	7·83	−1·91
Vibrn.	9·99	3·86	6·13	2·27	3·21	−0·94
Total	39·61	29·66	9·95	8·63	11·81	−3·18
			n-*Propyl* (*average*)			
Transl.	16·35	14·86	1·49	0·44	0·77	−0·33
Rotn.	13·27	10·84	2·43	5·92	7·73	−1·81
Vibrn.	9·99	4·09	5·90	2·27	3·44	−1·17
Total	39·61	29·79	9·82	8·63	11·74	−3·31
			iso*Butyl* (anti-*conformation*)			
Transl.	16·55	15·19	1·36	0·64	1·10	−0·46
Rotn.	13·78	12·01	1·77	6·43	8·90	−2·47
Vibrn.	10·20	4·42	5·78	2·48	3·77	−1·29
Total	40·53	31·62	8·91	9·55	13·77	−4·22
			iso*Butyl* (*D*- or *L*-syn-*conformation*)			
Transl.	16·55	15·19	1·36	0·64	1·10	−0·46
Rotn.	13·78	12·16	1·62	6·43	9·05	−2·62
Vibrn.	10·20	5·03	5·17	2·48	4·38	−1·90
Total	40·53	32·38	8·15	9·55	14·53	−4·98
			iso*Butyl* (*average*)			
Transl.	16·55	15·19	1·36	0·64	1·10	−0·46
Rotn.	13·78	12·11	1·67	6·43	9·00	−2·57
Vibrn.	10·20	4·82	5·38	2·48	4·17	−1·69
Total	40·53	32·12	8·41	9·55	14·27	−4·72
			neo*Pentyl*			
Transl.	16·74	15·48	1·26	0·83	1·39	−0·56
Rotn.	14·30	12·99	1·31	6·95	9·88	−2·93
Vibrn.	9·69	5·38	4·31	1·97	4·73	−2·76
Total	40·73	33·85	6·88	9·75	16·00	−6·25

of influences in the following figures (cal. deg.$^{-1}$ mole^{-1}), noting that a methyl and halogen which are *anti*-related in *syn*-Bu^{i}, become *syn*-related in the *anti*-isomer:

anti-Pr^{n}, 2·62; *syn*-Pr^{n}, 2·33. *syn*-Bu^{i}, 1·62; *anti*-Bu^{i}, 1·77.

The third ponderal effect is on vibrational entropy, and will cause the vibrational entropy of activation to decrease as new masses are added, except possibly when sufficient are introduced near the reaction centre. Added to this, there are steric effects in either direction on vibrational entropy, inasmuch as outward pressure on the reagent will increase the vibrational entropy of activation, whilst lateral pressure will decrease it. Our figures, given below (cal. deg.$^{-1}$ mole^{-1}), do not enable these effects to be clearly sorted out in every case: but they do show the ponderal retarding factor substantially in isolation in the difference from ethyl to *n*-propyl, the steric effects of which are identical; and they show the importance of the accelerating factors strikingly in the figure for *tert.*-butyl:

Me, 7·07; Et, 6·21; Pr^{n}, 5·90; Pr^{i}, 5·93; Bu^{i}, 5·38; Bu^{t}, 9·33; *neo*Pe, 4·31.

Conformational isomerism involves conflicting effects on vibrational entropy, for reasons analogous to those discussed above; but it happens that in both the examples for which we have calculated it, the vibrational entropy of activation increases with those conformational changes which predominantly bring remote masses closer, as the following figures show (cal. deg.$^{-1}$ mole^{-1}):

anti-Pr^{n}, 5·43; *syn*-Pr^{n}, 6·13. *syn*-Bu^{i}, 5·17; *anti*-Bu^{i}, 5·78.

It is of interest completely to separate the ponderal and the steric effect on entropy in order to see more clearly how each depends on structure. For the transition states, we can do this by recalculating their entropy with the supposition that all have the same energy surface as the methyl transition state, an assumption which excludes effects of steric hindrance. The translational entropies then remain unchanged; for they are in any case modified by structure only through the ponderal effect. The rotational entropies are changed slightly; for, in the absence of the imposed restriction, their structural modification is mainly ponderal, though it contains a very small steric element. On the other hand, the vibrational entropies, which, in the natural case, are modified by both the ponderal and the steric effect to an important degree, are considerably changed when the steric effect is thus artificially removed. The transition-state entropies, as they would be under the ponderal effect as the only structural influence, are shown in Table 14.

TABLE 14. *Calculated entropies (in cal. deg.$^{-1}$ mole^{-1}) for transition states of the bimolecular substitution,* $Br^- + RBr \longrightarrow BrR + Br^-$, *with the ponderal effect as the only structural influence, steric effects being excluded.*

R:	Me	Et	Pr^{i}	Bu^{t}	Pr^{n}	Bu^{i}	*neo*Pe
			Details of the vibrational entropy.				
Vib. z_t	3·12	3·12	3·12	3·12	3·12	3·12	3·12
,, x_t	2·24	2·79	3·09	3·31	3·09	3·31	3·45
,, y_t	2·24	2·19	2·13	3·31	2·19	2·19	2·19
,, x_a	0·06	1·61	1·21	2·10	2·39	2·67	3·01
,, y_a	0·06	0·06	2·06	2·10	0·06	0·06	0·06
			Parts of the total entropy				
Translation	15·91	16·14	16·35	16·55	16·35	16·55	16·74
Rotation	7·35	11·96	12·83	10·98	13·17	13·69	14·02
Vibration	7·72	9·77	11·61	13·94	10·76	11·35	11·83
			Total entropy				
	30·98	37·87	40·79	41·47	40·28	41·59	42·59

We can now isolate the ponderal effect on the entropies of the transition states by subtracting the entropy terms for the methyl group from corresponding terms for the higher alkyl groups. This is done in the uppermost part of Table 15. By subtracting

these figures from corresponding figures for the combined ponderal and steric effects on the entropy of transition states, as given in Table 13 (column 5), we isolate the steric effect on the entropies of the transition states. These values are in the central part of Table 15; and, at the foot of the Table, a summary is given of the ponderal and the steric contributions.

TABLE 15. *Calculated ponderal and steric effects (in cal. deg.$^{-1}$ mole^{-1}) on the entropy of transition states of the bimolecular substitutions,* $Br^- + RBr \longrightarrow BrR + Br^-$.

R:	Me	Et	Pr^i	Bu^s	Pr^n	Bu^i	*neo*Pe
Details of the ponderal contribution							
Translation	0·00	0·23	0·44	0·64	0·44	0·64	0·83
Rotation	,,	4·61	5·38	3·63	5·82	6·34	6·67
Vibration	,,	2·05	3·89	6·22	3·04	3·63	4·11
Details of the steric contribution							
Rotation	0·00	0·07	0·05	0·07	0·10	0·09	0·28
Vibration	,,	−0·73	−1·57	0·76	−0·77	−1·15	−2·14
Summary of the contributions							
Ponderal	0·00	6·89	9·71	10·49	9·30	10·61	11·61
Steric	,,	−0·66	−1·52	0·83	−0·67	−1·06	−1·86
Total	0·00	6·23	8·19	11·32	8·63	9·55	9·75

We see that the ponderal effect is positive, and increases with molecular weight. Amongst isomers, it shows only small changes of no consistent trend. This is because, although in accordance with the considerations indicated earlier, the rotational part becomes less positive with increased α-branching, the vibrational part shows opposing differences, largely for the reason that in some of the vibrations, y_a particularly, we do not, as already explained, regard the whole alkyl group as coupled in its motion with that of the halogens. We see that the steric effect varies as we should expect from qualitative inspection of the energy surfaces, being positive for the *tert.*-butyl group, and negative for all other groups.

Turning to the initial states, the situation is simple in that our calculations do not show that they suffer appreciable steric deformation. Therefore the entropies of initial states, as entered in Table 13 (column 3), are structurally modified through the ponderal effect only; and the structural modifications, as given in Table 13 (column 5), accurately represent the ponderal modifications.

By subtracting the initial-state entropies of Table 13 (column 3) from the transition-state entropies of Table 14, we obtain entropies of activation as they would be in the absence of a steric effect. The values are in Table 16. It should be noted that, although in most stable molecules vibrational entropies are considerably smaller than either translational or rotational entropies, this is not altogether true for transition states, because of the ease of deformation of the semi-bonds, and therefore it is not true for entropies of activation.

TABLE 16. *Calculated entropies of activation (in cal. deg.$^{-1}$ mole^{-1}) for the bimolecular substitution,* $Br^- + RBr \longrightarrow BrR + R^-$, *with the assumption that the ponderal effect is the only structural effect.*

R:	Me	Et	Pr^i	Bu^s	Pr^n	Bu^i	*neo*Pe
Translation	1·82	1·64	1·49	1·36	1·49	1·36	1·26
Rotation	4·24	3·10	1·84	1·25	2·33	1·58	1·03
Vibration	7·07	6·94	7·50	8·57	6·67	6·53	6·45
Total	13·13	11·68	10·83	11·18	10·49	9·47	8·74

If we subtract the methyl entropy terms of Table 16 from corresponding terms for the higher alkyl groups, we isolate the ponderal effect on entropy of activation. These values are in the top section of Table 17. By subtracting them from the corresponding values

for the combined ponderal and steric effect on entropy of activation, as given in Table 13 (last column), we isolate the steric effect on this quantity. These figures are in the central part of Table 17. The summary of this analysis is at the foot of the Table. It shows that the ponderal effect on the frequency factor of reaction rate is always retarding. The steric effect is accelerating for the *tert.*-butyl group, but is otherwise retarding, becoming more so as we ascend either the α- or β-methylated homologous series.

TABLE 17. *Calculated components of the structural effect on the entropy of activation (in cal. deg.$^{-1}$ mole^{-1}) of the bimolecular substitution* $Br^- + RBr \longrightarrow BrR + Br^-$.

R:	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
			Details of the ponderal effect				
Translation	0·00	−0·18	−0·33	−0·46	−0·33	−0·46	−0·56
Rotation	,,	−1·14	−2·40	−2·99	−1·91	−2·66	−3·21
Vibration	,,	−0·13	0·43	1·50	−0·40	−0·54	−0·62
			Details of the steric effect				
Rotation	0·00	0·07	0·05	0·07	0·10	0·09	0·23
Vibration	,,	−0·73	−1·57	0·76	−0·77	−1·15	−2·1
			Summary of the contributions				
Ponderal	0·00	−1·45	−2·30	−1·95	−2·64	−3·66	−4·39
Steric	,,	−0·66	−1·52	+0·83	−0·67	−1·06	−1·86
	0·00	−2·11	−3·82	−1·12	−3·31	−4·72	−6·25

(c) *Comparison of Effects of Alkyl Structure on Experimental Arrhenius Frequency Factors with Calculated Structural Effects on Entropies of Activation.*—With the usual convention of taking separate account of the entropy of motion in the reaction co-ordinate, so that this term can be omitted from the reckoning of transition-state entropies, the relation between the Arrhenius frequency factor B and the entropy of activation $S^\ddagger$ for a bimolecular reaction between ideal solutes is

$$\ln B = S^\ddagger/\boldsymbol{R} + \ln (\boldsymbol{k}T/\boldsymbol{h}) + 1$$

(Glasstone, Laidler, and Eyring, " Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 199).

With the aid of this formula, and of our calculations of the entropy of activation of the parent reaction of bromine-exchange

$$Br^- + MeBr \longrightarrow BrMe + Br^-$$

together with the experimental measurement of its Arrhenius frequency factor, we can estimate the theoretically unevaluated contribution of solvation to the entropy of activation of bromine-exchange in acetone. From the calculated part of the entropy of activation which is entered in Table 13, and the calculated translational entropy of the bromide ion, we find $S_G^\ddagger = -0{\cdot}45$ cal. deg.$^{-1}$ mole^{-1} as the entropy of activation of the reaction in the gaseous state. Introduction of this into the above equation shows that, at the standard temperature, the Arrhenius frequency factor of the gaseous reaction should be given by $\log_{10} B = 13{\cdot}13$. The observed frequency factor for the reaction in acetone is expressed by $\log_{10} B = 10{\cdot}7$. Insertion of this into the equation leads to an entropy of activation $S^\ddagger = -11{\cdot}6$ cal. deg.$^{-1}$ mole^{-1}. The difference between this and the gaseous value is $S_S = -11{\cdot}15$ cal. deg.$^{-1}$ mole^{-1}; and this represents the contribution of solvation, including any salt effect, to the entropy of activation of the reaction in acetone.

Our main object, however, is to compare calculated and observed effects of alkyl structure on the frequency factors of the substitutions; and, for this purpose, we need the above equation only in difference form,

$$\Delta \ln B = \Delta S^\ddagger/\boldsymbol{R}, \text{ or } \Delta \log_{10} B = \Delta S^\ddagger/4{\cdot}575$$

with $\Delta S^\ddagger$ in cal. deg.$^{-1}$ mole^{-1}, the temperature being standard.

With the observed and calculated values taken from Tables 11 and 13, respectively,

this comparison works out as shown in Table 18. There it is made in two ways, first, with the calculated figures for the bromine-exchange reaction, which is the only Finkelstein substitution for which they are as yet wholly available, and the observed values for the same reaction; and then, in view of the already noticed absence of any trend in the observed values, when, for any alkyl group, the halogens are changed, we compare the calculated figures for bromine-exchange with the averages, for common alkyl groups, of all the measured values.

TABLE 18. *Comparison of observed and calculated effects of alkyl structure on the logarithms of the Arrhenius frequency factors* ($\Delta\log_{10} B$).

	Me	Et	Pr^{i}	Bu^{s}	Pr^{n}	Bu^{i}	*neo*Pe
Obsd. (Br-exchange reaction)...	0·0	−0·6	−1·0	±0·0	−0·9	−1·1	−2·1
Calc. ,, ,, ...	0·0	−0·46	−0·84	−0·24	−0·72	−1·03	−1·37
Obsd. (all reactions: means)...	0·0	−0·5	−1·1	−0·2	−0·7	−1·1	−1·6

It will be seen that the calculated frequency factors put all the alkyl groups in the right order, with *tert.*-butyl most like methyl,* *neo*pentyl most unlike, and *iso*propyl and *iso*butyl similar to each other, with respect to effects on the frequency factor. Further, in most cases the calculations account nearly quantitatively for the observed values.† The main exceptions are the *tert.*-butyl group, for which the calculated frequency factor seems to be slightly too negative, and the *neo*pentyl group for which it is considerably too positive. We think that these discrepancies are due to theoretical over-simplification, most probably to the assumption of stiff alkyl groups. If there is indeed any appreciable compression energy in the initial states of the alkyl halides, despite the fact that calculations by our method find scarcely any, then the *tert.*-butyl group has more entropy of activation to gain than has any other group from the circumstance that, in the transition state, its component parts open like flower petals, so that any previously self-imposed restrictions in the group on its internal movement are relaxed, and the transition state is thus afforded some unreckoned additional entropy. Such an effect of any initial-state compression, if appreciable at all, must be small, even for *tert.*-butyl: it will be considerably smaller, and hence probably unnoticeable, for *iso*propyl; and it will be vanishing in every other case. On the other hand, the *neo*pentyl group indubitably has entropy of activation to lose, and much more to lose than has any other group, from the circumstance that its main parts are not only not spread out in the transition state, but must be considerably squeezed together by the outstandingly strong pressures there developed, with the result that new restrictions will be placed on the internal movements of the group, and the transition state will accordingly suffer an unreckoned loss of entropy. This undoubtedly real effect will be much smaller in all other groups, the calculated compression energies of which are all quite small in comparison with those of the *neo*pentyl group; and therefore the effect might well pass unnoticed in our results in all cases except that of the *neo*pentyl group. With these explanations we feel that Table 18 largely vindicates the method of our calculations, apart from the one assumption of stiff alkyl groups, which is regretfully made only for the abbreviation of arithmetic.

(E) Observed Effects of Alkyl Structure on Reaction Rate and their Comparison with Calculated Values.

(a) *Observed Rates of Seven Bimolecular Finkelstein Substitutions with Seven Alkyl Groups.*—The rates in acetone at 25° of the various substitutions, our experimental study of which is reported in the seven preceding papers, are collected in Table 19. As many of these rates are obtained by interpolation, and some by extrapolation, from observations made at other temperatures, no more than two-figure accuracy is intended by the entries.

We note that, if one halogen is kept fixed while the other is changed, then, no matter

* The peculiar position of the *tert.*-butyl group with respect to frequency factor in bimolecular substitutions was first noticed by Le Roux, Lu, Sugden, and Thompson (*J.*, 1945, 586), who described it as indicating an effective collision area too large to be understood on the basis of the theories of the time.

† The observational error in $\log_{10} B$ is about 0·1.

whether the variable halogen is that of the alkyl halide or that of the halide ion (and, indeed, it would be hard to say from these figures to which type of halogen variation the reaction rate is generally more sensitive), rate always increases from Cl to Br, and nearly always,* though by a much smaller factor, from Br to I. Our previous analysis of these rate changes in terms of variations of the Arrhenius energies of activation and the frequency factors showed that, whilst the rate changes of something over 10^2 from RCl to RBr,

TABLE 19. *Experimentally found second-order rate constants* (10^5k_2, *with* k_2 *in sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *for Finkelstein substitutions in acetone at 25°.*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
(1) $Cl^- + RCl$	3·9	0·050	—	—	—	—	—
(2) $Cl^- + RBr$	600	9·9	0·13	0·029	6·4	1·5	0·00026
(3) $Cl^- + RI$	470	42	1·3	—	25	1·6	0·00058
(4) $Br^- + RBr$	13,000	170	1·8	0·51	110	5·7	0·0026
(5) $Br^- + RI$	27,000	1490	37	—	1050	32	—
(6) $I^- + RBr$	25,000	170	1·3	0·10	140	6·0	0·0020
(7) $I^- + RI$	—	6000	53	18	—	—	0·11

illustrated by the first two rows in the Table, are due mainly to changes in the energy of activation, the remaining rate variations, covering a factor of something under 10^3, from the second row to the bottom of the Table, are attributable mainly to changes in the frequency factor. It would appear, therefore, that the rate variations down the columns of Table 19 are due, except where bound chlorine is involved, less to any energetic differences in the difficulty of securing the electron transfers from the halide ion to carbon and thence to the displaced halogen atom, than to effects of entropy, *i.e.*, to differences in the mass, shape, and stiffness of the reacting system, including its solvation shell. This is consistent with our preconception that the halogens are closely grouped in polarity.

For the purpose of considering the variations of reaction rate which occur when the halogens are kept the same whilst the alkyl group is varied, it is convenient to work with Table 20, in which the rates are re-expressed on a relative basis: for each type of Finkelstein substitution, the rate of the reaction of the ethyl group is taken as the unit, ethyl being chosen because it is the one group which is commom to both the α- and the β-methylated homologous series.

TABLE 20. *Found relative rates of Finkelstein substitutions in acetone at 25°.*

R	Me	Et	Pr^i	Bu^t	Pr^n	Bu^i	*neo*Pe
(1) $Cl^- + RCl$	71	1	—	—	—	—	—
(2) $Cl^- + RBr$	61	1	0·013	0·0029	0·65	0·15	0·000026
(3) $Cl^- + RI$	11	1	0·032	—	0·58	0·038	0·000014
(4) $Br^- + RBr$	76	1	0·011	0·0030	0·65	0·033	0·000015
(5) $Br^- + RI$	18	1	0·025	—	0·71	0·021	—
(6) $I^- + RBr$	140	1	0·0078	0·0051	0·82	0·036	0·000012
(7) $I^- + RI$	—	1	0·0088	0·0030	—	—	0·000018

The picture here is of a fall of rate along the α-series, Me, Et, Pr^i, Bu^t, in two moderate steps, followed by a third much smaller one; and of a fall along the β-series, Et, Pr^n, Bu^i, *neo*Pe, in steps which grow successively steeper with rising intensity. The preceding discussion shows that, in the α-series, the smallness of the third step is due to the sudden restoration of the original symmetry at the end of the series, a restoration which superposes an entropic factor of steric acceleration on a ponderal entropy factor of retardation, and on the still-growing energetic factor of combined polar and steric retardation. We have seen also that, along the β-series, the entropy change alone accounts for the first small step, whilst entropy and energy effects both contribute to the succeeding steps, the last of which illustrates the characteristically sudden way in which steric hindrance becomes important, by reason of its energetic factor, as congestion in the system is progressively increased.

* The one apparent anomaly would undoubtedly disappear if salt conditions could be standardised down the columns of the Table, as they are along its rows (cf. p. 3224).

(b) *Calculated Structural Effects on the Rates of Finkelstein Substitutions and their Comparison with Observed Reaction Rates.*—Going beyond a qualitative description of the involved factors, as in the preceding paragraph, our discussions of Sections C and D solve quantitatively (though not with all the precision we would like) the two parts of the problem of accounting for structural effects on the rates of our reactions. And so it is of interest to put these parts together, and to see how closely their combination matches the experimental observations.

This synthesis and comparison is made comprehensively in Fig. 4, in which the scales of ΔE_A, $\Delta \log_{10} B$, and $\Delta \log k_2^{25}$ are so adjusted as to show directly the relative importance of the variations of activation energy and of frequency factor in the determination of the

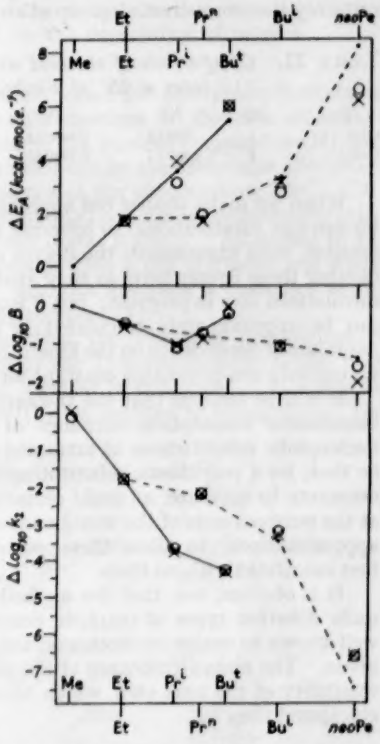


FIG. 4. *Calculated and observed effects of alkyl structure on the rates, and their energetic and entropic factors, of Finkelstein substitutions. In each part of the diagram, the same vertical height (apart from sign) corresponds to the same change in the free-energy of activation. The lines are theoretical: they join calculated points for the bromine-exchange reaction, and also the practically coincident points representing average values calculated for the seven Finkelstein substitutions. The points marked × denote the observed values for the bromine-exchange, and those marked ○ represent means of observed values for all the substitutions.*

rate relations. We can at present give theoretical rate values accurately and completely only for the bromine-exchange reaction, for which alone the entropy calculations have been finished: calculated frequency factors from Table 18, and calculated energy increments from Table 9, are combined in the Arrhenius equation. However, we can make similar, though only approximate, rate calculations for all the Finkelstein substitutions, employing throughout the entropy values calculated for the bromine exchange, and using, for the three symmetrical substitutions, the directly calculated energy values, and for the four unsymmetrical substitutions, energies interpolated as well as may be between the fairly close-lying values calculated for the symmetrical reactions. Most of the figures fall into such close groups that it is not possible to represent them all in one diagram; and therefore Fig. 4 compares, for each alkyl group, first, the calculated with the experimental values for the bromine-exchange reaction, and, secondly, the averages of the calculated values for all the seven reactions with the averages of all the available observed values for these reactions. The lines join points calculated for the bromine exchange; and equally they

join the points which represent the averages of calculated values, these points falling too close to the others to be shown separately. About these dual-purpose theoretical lines are entered the two sets of observational points, for which the data come from Tables 11, 6, and 20: one set is for the bromine exchange, whilst the other represents means of the observations made on all reactions of the series.

For closer assessment of the numerical performance of the theory in the calculation of structural effects on rate, Table 21 is given, in which calculated relative rates for the bromine-exchange reactions are compared with the corresponding observational values, derived from the figures in Table 19. It will be seen that the calculated rate figures are good to a factor of 2·5 over that range, 23,000, of rates which excludes the *neo*pentyl group, and to a factor of 5·5 over the complete range of 5,000,000 which includes that group, certainly the worst-treated group of any by the approximations we have had to make.

TABLE 21. *Comparison of observed and calculated effects of alkyl structure on the relative rates at 25° of Finkelstein bromine-exchange in acetone.*

R:	Me	Et	Pr^{i}	Bu^{s}	Pr^{n}	Bu^{i}	*neo*Pe
Obs.	1	0·013	0·00014	0·000039	0·0085	0·00044	0·00000020
Calc.	1	0·017	0·00035	0·000053	0·0090	0·00035	0·000000037

When we make similar but approximate calculations as indicated above, for the other Finkelstein substitutions, so covering 49 reactions in all, and compare the results, where possible, with experiment, the degree of agreement is quite similar. There is no point in quoting these figures here, as they are bound to be changed to some extent by the further calculations now in progress; but it is already clear that structural effects on reaction rate can be approximately calculated in large numbers from a known mechanism with a minimum of dependence on the kinetic observations themselves. In the present calculations we use only one disposable constant for the whole assembly of groups and reactions.

It will be obvious that the theoretical analysis which has been illustrated here for the bimolecular nucleophilic exchange of halogens, could be extended to any bimolecular nucleophilic substitutions at saturated carbon. The main complication in practice would be that, for a polyatomic substituting agent, or a polyatomic displaced group, it would be necessary to estimate, as could certainly be done in a rough way, the bending potentials at the outward ends of the semi-bonds of the transition state, and, proceeding by successive approximations, to allow these potentials to adjust transition-state configurations at first calculated without them.

It is obvious, too, that the method of analysis illustrated could be paralleled for some quite different types of reaction, provided, of course, that the mechanism is sufficiently well known to enable an electronic and geometrical description of its transition state to be given. The main significance of the present work may be that it indicates the nature and feasibility of the next step, which becomes possible when a reaction mechanism has been elucidated thus far.

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The Morphine–Thebaine Group of Alkaloids. Part III. The Structure of the Codeimethines, and Related Topics.*

By K. W. Bentley and A. F. Thomas.

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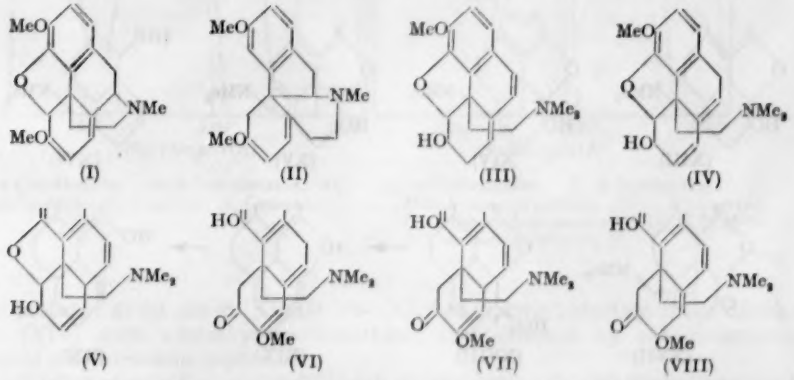
The structures adduced for α- and β-codeimethine by earlier workers have been confirmed and an alternative structure tentatively advanced for the α-isomer by Robinson disproved. A new α-dihydrocodeimethine has been prepared by the reduction of codeine methiodide and of α-codeimethine with sodium and liquid ammonia, reactions that also involve the production of a compound belonging to the deoxycodeine series. A new type of nitrogen-free substance has been prepared by the degradation of neopine dihydromethine.

In the arguments leading up to the now accepted structure for phenyldihydrothebaine Robinson (*Nature*, **1947**, **160**, 815) stated that the only structure for thebaine other than the accepted one (I) capable of explaining formation of the former compound is (II), and that this type of structure in the morphine series is ruled out by the ultraviolet absorption of β-codeimethine which is consistent with the presence of the chromophore Ph·C:C·C:C; this is in agreement with the structure (III) for this compound and cannot be accommodated on a spiran structure of type (II). At the same time it was stated: "According to Dr. Strauss the ultraviolet absorption spectrum of α-codeimethine is not styrenoid and would be consistent with the arrangement Ph·C·C:C·C:C," and this grouping is embodied in the structure (IV) for the α-isomer instead of the formerly accepted (V).

Now structure (IV) for α-codeimethine implies that the Hofmann degradation of codeine methiodide takes place under the influence of the 7 : 8-double bond rather than of the aromatic nucleus, which seems improbable. Further, a compound (IV) would be expected to isomerise readily in alkaline solution to (V) (cf. eugenol to *iso*eugenol). The

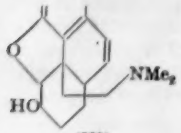


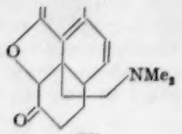
only previous case in which the three isomers of the types (III), (IV), and (V) have been isolated is in the degradation of sinomenine methiodide. There the tendency to give a 9 : 14 double bond under the influence of the C:C·CO system would be expected to be greater than with codeine methiodide, and the product (IV) would be expected to be more stable in alkali than (IV). In fact sinomenine *achro*methine (VI) is isolated only under carefully controlled conditions and is very readily isomerised to sinomenine *roseo*methine (VII) and sinomenine *violeo*methine (VIII) (Goto and Shishido, *Bull. Chem. Soc. Japan*, 1931, **6**, 79).

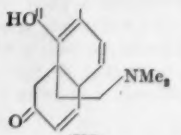
It is difficult to reconcile the structure (IV) for α-codeimethine with the production

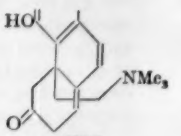
* Part II, *J.*, 1952, 972.

on mild reduction over nickel (von Braun and Cahn, *Annalen*, 1927, **451**, 55) of the same compound (IX) as is obtained by the degradation of dihydrocodeine methiodide (Freund, Melber, and Schlesinger, *J. prakt. Chem.*, 1920, **101**, 1), during which reaction it is inconceivable that the double bond appears at any position other than 9 : 10. One explanation of this could be that the compound (IV) is converted under the influence of the catalyst into its isomer (V), which is then reduced at the isolated double bond to (IX). In an attempt to realise this hypothetical isomerisation by heating α-codeimethine in alcoholic solution with Raney nickel, the products were dihydrocodeine methine (IX) and dihydro-


(IX)

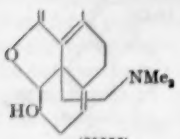

(X)

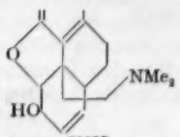

(XI)

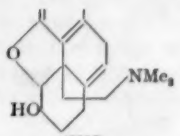

(XII)

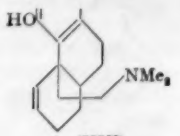
codeinone methine (X) (cf. the arrangement of codeine to dihydrocodeinone under the influence of noble metal catalysts; Knoll and Co., D.R.-P., 365,683/1921, 380,919/1922, 607,931, 617,238, 623,821/1934; *Friedlander*, **14**, 1301 1302; **21**, 652; **22**, 583, 584); a third, phenolic, substance, presumably thebainone-A methine (XI) (cf. the rearrangement of codeine to thebainone-A under slightly different conditions; Weiss and Weiner, *J. Org. Chem.*, 1949, **14**, 194) was also produced but proved so sensitive to aerial oxidation that isolation and purification was never achieved [cf. the sensitivity of thebainone-B methine (XII); Bentley, Robinson, and Wain, *J.*, 1952, 958; Bentley and Cardwell, following paper].

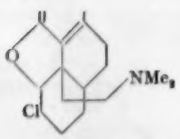
The reduction of α- and β-codeimethine with sodium and liquid ammonia was next investigated, as here the temperature precludes initial conversion of α- into β-methine. Under these conditions, (IV) would be expected to suffer 1 : 4-reduction of the conjugated system to give (XIII) whilst (V) and (III) would undergo reduction only of the double

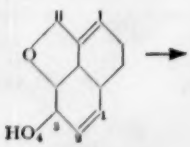

(XIII)

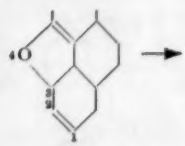

XIV)

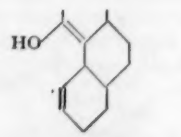

(XV)


(XVI)


(XVII)


(XVIII)

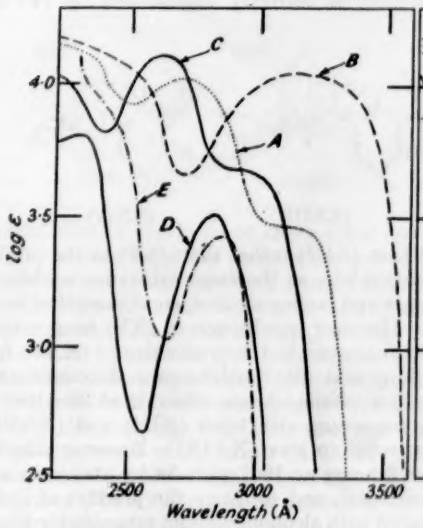

(XIX)


(XX)

bond conjugated with the aromatic nucleus, yielding (XIV) and (XIII) respectively. Alternatively (V) could undergo 1 : 4-reduction of the conjugated diene system, giving (XV). The sodium–ammonia reduction of β-codeimethine was expected to give the same product, (XIII) or (XV), as has already been obtained by the sodium and alcohol reduction of α-codeimethine (Vongerichten, *Ber.*, 1899, **32**, 1047; 1901, **34**, 2722), the mild catalytic (von Braun and Cahn, *loc. cit.*) and sodium amalgam (Mosettig, *J. Org. Chem.*, 1940, **5**, 401) reduction of β-codeimethine, and the sodium–ammonia reduction of neopine methiodide (Bentley and Wain, *J.*, 1952, 972), whilst the product (XIV) would be a new compound and should also be accessible by the sodium–ammonia reduction of codeine methiodide.

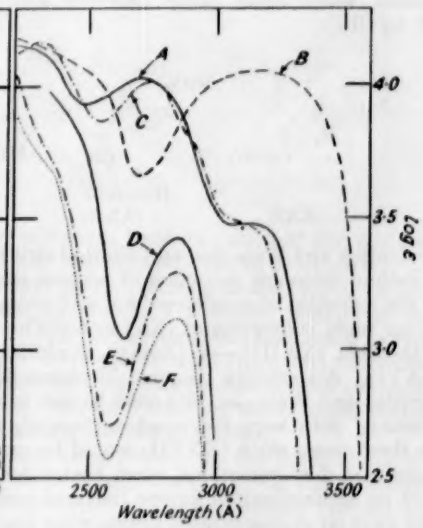
As expected, β-codeimethine was reduced in this way to give a good yield of the base (XIII) or (XV) whilst α-codeimethine gave 10—40% of a new base, codeine dihydromethine (α-dihydrocodeimethine-A) (XIV), and 40—60% of a phenolic substance, the amount of the former decreasing and of the latter increasing as the amount of sodium used for the reduction was increased. The same two compounds, with the same variation in yield, were obtained on reduction of codeine methiodide under the same conditions. The phenolic substance appears to be deoxydihydrocodeine-C dihydromethine (XVI) and may be identical with the compound prepared by Cahn (*J.*, 1926, 2562) by sodium–alcohol reduction of 6-chloro-α-tetrahydrocodeimethine (XVII), though Cahn appears to think the Δ^6-structure equally likely for his compound, and indeed the solubility properties of the two substances appear to be different. The mechanism for the production of (XVI) from

FIG. 1.



A, α-*Codeimethine*. *B*, β-*Codeimethine*. *C*, iso*Eugenol*. *D*, *Eugenol*. *E*, *Codeine*.

FIG. 2.



A, α-*Codeimethine*. *B*, β-*Codeimethine*. *C*, *Dihydrocodeine methine* (IX). *D*, *Codeine*. *E*, *Codeine dihydromethine* (XIV). *F*, $\Delta^{9(14)}$-*Dihydrocodeimethine* (XV).

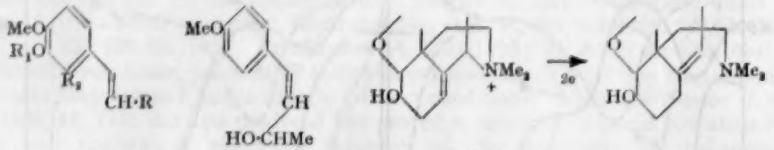
(XIV) is probably as set out in (XVIII) ⟶ (XX). Catalytic reduction of the dihydromethine (XIV) gave α-tetrahydrocodeimethine, also obtained by sodium–ammonia reduction of dihydrocodeine methiodide.

The reduction of morphine methiodide with sodium, ammonia, and alcohol apparently follows a similar course, giving a catechol derivative, the isolation of which from the resulting alkaline solution proved impossible owing to the excessively rapid aerial oxidation (cf. *apo*morphine in alkaline solution). By reasoning from the above, codeine on reduction in the same way would be expected to give first deoxycodeine-C and finally deoxydihydrocodeine-C, but only codeine and the merest trace of phenolic matter could be recovered from this reduction. The sodium–ammonia reduction of 6-acetyl*neo*morphine methiodide apparently gives the morphine analogue of (XIII), but this could not be characterised.

The results of these reductions favour the structure (V) rather than (IV) for α-codeimethine and the ultraviolet absorption spectra do in fact confirm this. Fig. 1 shows the spectra of α-codeimethine, β-codeimethine, codeine, eugenol, and *iso*eugenol. The spectra

of the codeine derivatives show a slight shift to longer wavelengths in comparison with eugenol and *iso*eugenol, but that of α-codeimethine is clearly analogous to that of *iso*eugenol and not to that of eugenol. Further Braude (personal communication) points out that the chromophore of α-codeimethine is (XXI) and the maxima are at 2750 and 3100 Å; for the analogous alcohol (XXII) the maxima are at 2610 and 2920 Å (Braude, *J.*, 1947, 1087); introduction of the *m*-alkoxy- and the *o*-alkyl substituent displaces the two bands by 140 and 180 Å respectively. Such shifts do not appear to be unusual if (XXII) and 2′-methylstyrylmethanol (Braude, *loc. cit.*, max. 2550 and 2880 Å) are compared with 1-styrylethanol (Braude, *loc. cit.*, max. 2510 and 2810 Å). In fact the combined shifts due to *p*-methoxy and *o*-methyl would be 100 + 40 = 140 Å and 100 + 70 = 180 Å on the shorter and longer-wavelength bands respectively, in exact agreement with the figures above.

Furthermore Fig. 2 gives the spectra of α-codeimethine, β-codeimethine (III), codeine dihydromethine (XIV), the base (XV) (see below), dihydrocodeine methine (IX) and codeine, which again prove that the α-methine is correctly represented by (V) and not by (IV).

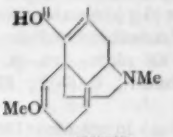


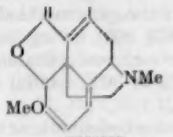
(XXI) (XXII) (XXIII) (XXIV)

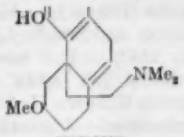
Bentley and Wain (*loc. cit.*) allotted structure (XIII) rather than (XV) to the product of sodium–ammonia reduction of neopine methiodide, as the same substance is obtained by the reduction of α-codeimethine with sodium and boiling alcohol, conditions that would favour rapid conversion of (XV) into (IX). However, production of (XV) from neopine methiodide, (XXIII) ⟶ (XXIV), would be analogous to the production of (XXV) from (XXVI). Accordingly neopine dihydromethine and dihydrothebaine-φ dihydromethine (Bentley and Wain, *loc. cit.*) were heated with alcoholic sodium ethoxide at 90—100° for 8 hours; both were recovered unchanged, suggesting structures (XIII) and (XXVIII) for these bases since (XXVII) would be expected to give (XXIX). However dihydrothebaine-φ dihydromethine, when heated for 3 hours at 100° with 5N-hydrochloric acid, gave no αβ-unsaturated ketone (infrared spectrum), and similarly the product of hydrolysis gave no αβ-unsaturated ketone when heated with alcoholic sodium ethoxide for 1 hour. These results indicate that the product of hydrolysis of dihydrothebaine-φ dihydromethine is not an αβ-unsaturated ketone; it is accordingly allotted structure (XXX) rather than (XXXI); dihydrothebaine-φ dihydromethine is therefore (XXVII), and neopine dihydromethine is (XX). The infrared spectrum of dihydrothebaine-φ dihydromethine supports this conclusion, for it differs from that of dihydrothebaine-φ in the region 5·8—7·0 μ and in particular does not show the bands at 5·9 and 6·0 μ characteristic of the 1 : 4-dihydroanisole system (see Stork, *J. Amer. Chem. Soc.*, 1952, **74**, 768). It is now easier to understand why it was found much more difficult to hydrogenate dihydrothebaine-φ dihydromethine (XXVII) and the product of hydrolysis (XXX) than to hydrogenate dihydrothebaine-φ (XXV) and thebainone-B (XXXII) (Bentley and Wain, *loc. cit.*). The structures of other degradation products prepared by Bentley and Wain must similarly be revised.

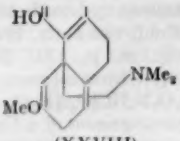
As previously stated (Bentley and Wain, *loc. cit.*) the degradation of the methiodide of (XV) by sodium *cyclo*hexyloxide in boiling *cyclo*hexanol affords a mixture, now shown by chromatography to consist of methylmorphenol (*ca.* 20%), a nitrogen-free substance of structure (XXXIII) or (XXXIV) (*ca.* 50%), and a by-product from the *cyclo*hexanol series (*ca.* 25%). The structure (XXXIII) or (XXXIV) was allotted to the major product, for its ultraviolet absorption closely resembles that of α-codeimethine, indicating the conjugation of one double bond with the nucleus, and also the infrared absorption indicates the presence of a hydroxyl group.

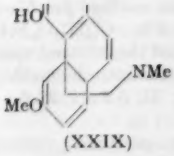
Attack at the carbon atom β to the nitrogen by a *cyclo*hexyloxide ion probably results in elimination of the side-chain to give (XXXIII, but $\Delta^{8(14)}$); migration of the double bond into the *iso*eugenol position followed by the addition of a proton would then afford (XXXIII). This structure is regarded as the most probable, for the tendency for the double bond to migrate to the 13 : 14-position may well be the real driving force behind the elimination of the side-chain. Alternatively the double bond could migrate to the 9 : 10-position, this being followed by elimination of the side-chain to give (XXXIV). It may

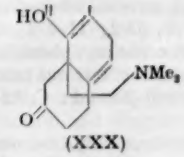

(XXV)

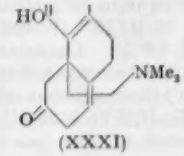

(XXVI)

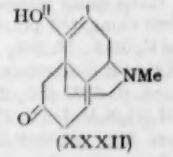

(XXVII)


(XXVIII)


(XXIX)

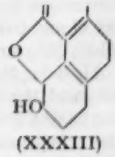

(XXX)

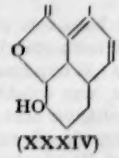

(XXXI)

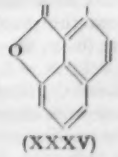

(XXXII)

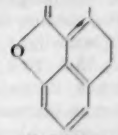
be noted that in this type of elimination the side-chain becomes joined at the β-carbon atom to the reacting anion by an ether link as was originally believed to be the case in the degradations of substances with a free 4-hydroxyl group, resulting in the thebenone type of cyclic ether (Bentley, Robinson, and Wain, *loc. cit.*).* The second product of this elimination reaction would be $C_6H_{11}\cdot O\cdot CH_2\cdot CH_2\cdot NMe_3\}I$, which could then suffer normal Hofmann degradation to give trimethylamine and *cyclo*hexyl vinyl ether, and indeed the by-product of the degradation, clearly still a mixture, appears to contain this substance contaminated with *cyclo*hexanol, as the infrared absorption obtained shows bands characteristic of the groupings C·O·C:C (9·43μ) and ·CH:CH_2 (10·32 and 10·88μ).

The compound of structure (XXXIII) would be expected, on the basis of Emde's conclusions (*Helv. Chim. Acta*, 1930, **13**, 1035), to be lævorotatory, whereas the compound of structure (XXXIV) might be dextro- or lævo-rotatory. The degradation product was strongly dextrorotatory.


(XXXIII)


(XXXIV)


(XXXV)


(XXXVI)

Methylmorphenol (XXXV) could arise from (XV) by normal Hofmann degradation, dehydration, and extrusion of the 13-vinyl group, giving the diphenyl (XXXVI), followed by aerial oxidation.

Treatment of neopine hydrobromide in formic acid with hydrogen peroxide afforded 1-bromoneopine; an attempt to prepare 1-bromothebaine in a similar way from thebaine hydrobromide yielded 14-hydroxycodeinone.

* The thebenone type of substance is now believed to contain a six-membered cyclic ether system (Rapoport, *J. Amer. Chem. Soc.*, 1953, **75**, 5329; Bentley and Cardwell, unpublished results), but the later results scarcely justify a dogmatic assertion "*in the absence of further evidence*" by Stork (*loc. cit.*) that they contain six-membered ethers. *In the absence of further evidence* all that could then be said was that no evidence was available to decide between the five- and the six-membered ether structures.

Experimental

α-Codeimethine, prepared by degradation of codeine methiodide, formed rods, m. p. 118·5° (lit., 119°), on recrystallisation from aqueous ethanol. The *perchlorate* was obtained as prisms, m. p. 183°, from 90% ethanol, $[\alpha]_D^{26}$ −116·4° (2% in H_2O) (Found: C, 55·0; H, 6·0. $C_{19}H_{23}O_3N,HClO_4$ requires C, 55·2; H, 5·9%).

Small (*J. Org. Chem.*, 1947, **12**, 359) reports that neopine methiodide is recovered unchanged from hot alcoholic potassium hydroxide. However we found that degradation is rapid when 35% sodium hydroxide solution (150 ml.) is added to neopine methiodide (5 g.) in water (250 ml.) at 100° (cf. van Duin, Robinson, and Smith, *J.*, 1926, 903), giving β-codeimethine, prisms (from ethanol), m. p. 134° (lit., 134°). The *perchlorate*, was obtained as plates, m. p. 152° (decomp.), from aqueous ethanol, $[\alpha]_D$ +242° (2% in 50% EtOH) (Found: C, 54·2; H, 5·6. $C_{19}H_{23}O_3N,HClO_4,\frac{1}{2}H_2O$ requires C, 54·0; H, 5·2%).

Rearrangement of α-Codeimethine.—A solution of α-codeimethine (10 g.) in ethanol (100 ml.) was neutralised to litmus with hydrochloric acid and boiled with Raney nickel (5 g.) for 2 hr., the solution filtered, and perchloric acid (5 ml.) added. Mauve-coloured crystals separated which, three times crystallised from 50% ethanol, gave *dihydrocodeinone methine perchlorate* as colourless elongated plates, m. p. 267° (Found: C, 55·2; H, 5·8; Cl, 8·9. $C_{19}H_{23}O_3N,HClO_4$ requires C, 55·2; H, 5·8; Cl, 8·6%). The substance was non-phenolic and the infrared spectrum showed that it is a ketone. The base was not crystalline, but was converted into the methiodide, prisms, m. p. 282° (lit., 280°) (from aqueous ethanol) (Found: C, 52·7; H, 5·7; I, 27·6. Calc. for $C_{19}H_{23}O_3N,MeI$: C, 52·7; H, 5·7; I, 27·9%).

From the mother-liquors of the perchlorate, dihydrocodeine methine perchlorate gradually separated as prisms, m. p. 206° (lit., m. p. 203°) (Found: C, 55·3; H, 6·5. Calc. for $C_{19}H_{25}O_3N,HClO_4$: C, 55·0; H, 6·3%). The final mother-liquors left contained material almost wholly soluble in alkali (giving therein an intense red colour with diazotised sulphanilic acid), but the solution rapidly darkened in air, and the phenolic base could not be isolated. When this rearrangement was carried out without the addition of acid, the solution rapidly absorbed oxygen and became deep purple, with consequent diminution in yield.

Reduction of α-Codeimethine.—(*a*) Sodium (2 g.) was added in slices to a solution of α-codeimethine (5 g.) in liquid ammonia (350 ml.) and ethanol (50 ml.), with vigorous stirring. The mixture was poured into water (250 ml.), and the whole saturated with ammonium chloride and extracted three times with ether. The combined extracts were washed, dried, and evaporated, leaving a viscous oil. With 60% perchloric acid (2 ml.) in ethanol (18 ml.) this gave *codeine dihydromethine perchlorate* which, recrystallised three times from aqueous ethanol, was obtained as felted needles, m. p. 210°, $[\alpha]_D$ −33·4° (2% in H_2O) (Found: C, 54·7; H, 6·5; Cl, 8·3. $C_{19}H_{25}O_3N,HClO_4$ requires C, 55·0; H, 6·3; Cl, 8·6%). The base was an oil and was converted into the *methiodide*, prisms, m. p. 265° (from aqueous ethanol) (Found: C, 52·5; H, 6·3. $C_{19}H_{25}O_3N,MeI$ requires C, 52·5; H, 6·5%). Both salts differed in their infrared spectra from the neopine dihydromethine salts.

From the mother-liquors from the perchlorate a base was obtained as elongated plates, m. p. 158° [from light petroleum (b. p. 60—80°) and from ether], $[\alpha]_D$ +21·5° (2% in $CHCl_3$) (Found: C, 75·4, 75·3; H, 9·0, 9·2; N, 4·1. $C_{19}H_{27}O_2N$ requires C, 75·6; H, 9·0; N, 4·6%). This substance, *deoxydihydrocodeine-C dihydromethine*, was soluble in alkali, and the alkaline solution gave an intense red colour with diazotised sulphanilic acid. The base gave a green-blue colour with ferric chloride. It is readily soluble in organic solvents with the exception of low-boiling light petroleum. In this reduction 2 g. each of dihydrodeoxycodeine-C dihydromethine and codeine dihydromethine were obtained.

(*b*) α-Codeimethine (5 g.) was reduced as above with sodium (3 g.), ethanol (25 ml.), and liquid ammonia (300 ml.); 3·5 g. of dihydrodeoxycodeine-C dihydromethine and 1 g. of codeine dihydromethine were obtained.

(*c*) α-Codeimethine (5 g.) was reduced with sodium (5 g.), alcohol (50 ml.), and liquid ammonia (300 ml.); only dihydrodeoxycodeine dihydromethine (3·9 g.) was recovered.

Reduction of Codeine Methiodide.—(*a*) Codeine methiodide (10 g.) was reduced as above with sodium (4 g.), ethanol (150 ml.), and liquid ammonia (500 ml.); 4 g. of codeine dihydromethine and 2·5 g. of dihydrodeoxycodeine-C dihydromethine were obtained.

(*b*) Codeine methiodide 10 g.), reduced with sodium (15 g.), ethanol (200 ml.), and liquid ammonia (700 ml.), gave only dihydrodeoxycodeine-C dihydromethine (5 g.).

Reduction of β-Codeimethine.—β-Codeimethine (6 g.) was reduced with sodium (3 g.), ethanol

(25 ml.), and liquid ammonia. The oily product slowly solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave neopine dihydromethine as prisms, m. p. 88—89° (lit., 86—88·5), $[\alpha]_D$ −105° (1% in EtOH) (Found: C, 72·6; H, 8·0. Calc. for $C_{19}H_{23}O_3N$: C, 72·3; H, 8·0%). Neopine dihydromethine prepared by Bentley and Wain (*loc. cit.*) recrystallised readily when seeded with this product and had identical properties. The perchlorate of the base obtained by the reduction of β-codeimethine had m. p. 216° and the methiodide, m. p. 251—253°, both alone or mixed with the corresponding salts prepared by Bentley and Wain.

Reduction of Codeine Dihydromethine.—A solution of codeine dihydromethine (2 g.) in ethanol (50 ml.) was shaken with palladised strontium carbonate under hydrogen at room temperature and atmospheric pressure until absorption ceased. The catalyst and solvent were removed, leaving an oil, which afforded a perchlorate, prisms, m. p. 217° (from 90% ethanol), $[\alpha]_D$ −33·4° (2·5% in 50% EtOH) (Found: C, 53·5; H, 6·7. Calc. for $C_{19}H_{27}O_3N,HClO_4,\frac{1}{2}H_2O$: C, 53·5; H, 6·8%), and a methiodide, needles, m. p. 221° (from aqueous alcohol) (Found: C, 50·3; H, 6·7. Calc. for $C_{19}H_{27}O_3N,MeI,H_2O$: C, 50·3; H, 6·8%), both m. p.s being undepressed on admixture with the α-tetrahydromethine derivatives.

Reduction of Dihydrocodeine Methiodide.—Dihydrocodeine methiodide (8 g.) was reduced with sodium (5 g.), ethanol (100 ml.), and liquid ammonia (300 ml.) as described above; and the product (5 g.) consisted only of α-tetrahydrocodeimethine (perchlorate, prisms, m. p. and mixed m. p. 217°; methiodide, needles, m. p. and mixed m. p. 221°).

Reduction of Morphine Methiodide.—Morphine methiodide (10 g.) was reduced by sodium (10 g.), liquid ammonia (300 ml.), and ethanol (100 ml.). When all the methiodide had dissolved a red colour developed. This was destroyed as each fresh slice of sodium was added, but reappeared as soon as the sodium had completely dissolved. Pouring the ammoniacal solution into water gave a homogeneous solution which very rapidly darkened in air. No base was recovered.

Reduction of 6-O-*Acetylneomorphine Methiodide.*—6-*O*-Acetylneomorphine (6 g.) was converted into the *methiodide*, triangular and oblong prisms, m. p. 244°, $[\alpha]_D$ +24° (1·1% in H_2O) (Found: C, 51·5; H, 5·4. $C_{19}H_{21}O_4N,MeI$ requires C, 51·2; H, 5·2%), which was difficult to crystallise. The methiodide (5 g.) was reduced with sodium (0·75 g.) and liquid ammonia (150 ml.). The mixture was poured into saturated ammonium chloride solution, and the product extracted with chloroform. After removal of the chloroform the product was obtained as a dark brown gum, that was sublimed at 180°/0·08 mm., being then obtained as minute colourless crystals that very rapidly degenerated to an orange solid, m. p. *ca.* 18° finally giving a tar, on exposure to the air. No satisfactory analytical figure could be obtained for this substance, which is believed to be neomorphine dihydromethine. The picrate and methiodide were oils, and all the other salts appear to be very soluble in the solvents used for their preparation.

Degradation of Neopine Dihydromethine Methiodide.—Neopine dihydromethine methiodide (prepared from β-codeimethine) was degraded as described by Bentley and Wain (*loc. cit.*) to an oil (4 g.) that was passed in benzene (120 ml.) and light petroleum (b. p. 40—60°) down a column of activated alumina (70 g.). A wide band having a purple fluorescence was eluted from the column first, with 3 : 2 ⟶ 4 : 1 benzene–light petroleum (b. p. 40—60°); it was obtained as a white wax, which after further chromatography gave methylmorphenol, m. p. 60°, elongated prisms, m. p. 62° (undepressed on admixture with a specimen prepared from α-codeimethine) on recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 81·2; H, 4·3. Calc. for $C_{15}H_{16}O_2$: C, 81·1; H, 4·5%). The *picrate* was prepared in ethanol and obtained as red needles, m. p. 119°, decomposing on attempted recrystallisation and only stable in the presence of excess of picric acid.

From the original chromatogram a second product was eluted with solvents from benzene (90%) to pure benzene; it was a pale yellow oil (0·9 g.) with a pale blue fluorescence. On distillation it was colourless, b. p. 120°/0·05 mm., n_D^{20} 1·6518, $[\alpha]_D$ = 0·0° (Found: C, 79·1; H, 11·25%).

By elution from the column with solvents from pure benzene to 4 : 1 benzene–chloroform a third product was obtained as a non-fluorescent amber glass, b. p. 170°/0·02 mm. [Found: C, 73·3; H, 7·0%; *M* (Rast), 261. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%; *M*, 244]. This substance, believed to be (+)-1 : 2 : 3 : 4 : 9 : 10-*hexahydro*-3-*hydroxy*-6-*methoxy*-4 : 5-*phenanthrylene oxide*, is strongly dextrorotatory in chloroform, but the solution darkened and accurate reading of the rotation was impossible.

Attempted Isomerisation of Neopine Dihydromethine and Dihydrothebaine-ϕ *Dihydromethine.*—Neopine dihydromethine (2·4 g.) was heated at 90—100° with a solution of sodium (2·5 g.)

in ethanol (60 ml.) for 8 hr., and the mixture was cooled, diluted with saturated ammonium chloride, and extracted five times with ether. The ether extracts afforded 2·0 g. of a brown oil that crystallised on trituration with light petroleum and seeding with neopine dihydromethine. It was obtained as colourless prisms, m. p. 87—88° undepressed on admixture with the starting material, after recrystallisation from light petroleum (b. p. 60—80°). The ultraviolet spectra of the starting material and recovered base were identical.

Dihydrothebaine-ϕ dihydromethine behaved similarly.

Hydrolysis of Dihydrothebaine-ϕ Dihydromethine.—This methine (5·0 g.) was heated at 100° with 5N-hydrochloric acid (20 ml.) for 3 hr., the solution neutralised with ammonia, and the precipitated base collected, washed and recrystallised from aqueous alcohol. Only $\Delta^{9(14)}$-dihydrothebainone methine (thebainone-B dihydromethine of Bentley and Wain) was obtained as almost colourless needles, m. p. 164°. Neither the crude product nor the recrystallised material showed infrared bands characteristic of αβ-unsaturated ketones; the only ketone band was found at 5·86 μ. Only tar was recovered when this ketone was heated for 1 hr. with sodium ethoxide solution; the infrared spectrum of the tar showed no bands attributable to an αβ-unsaturated ketone system.

1-*Bromoneopine.*—Neopine hydrobromide (3 g.), 30% formic acid (50 ml.), and 30% hydrogen peroxide (2 ml.) were set aside overnight. On neutralisation the solution gave 1-bromoneopine which recrystallised from aqueous ethanol as prisms (becoming faintly pink in air), m. p. 174°, $[\alpha]_D$ −42·1° (2·5% in EtOH) (Found: C, 57·1; H, 5·4; Br, 21·3. $C_{18}H_{20}O_3NBr$ requires C, 57·1; H, 5·3; Br, 21·2%). The *hydrogen tartrate*, prepared in ethanol, recrystallised from 96% ethanol, as prisms, m. p. 248° (decomp.), $[\alpha]_D$ 0·0° (in H_2O) (Found: C, 49·7; H, 5·0; Br, 14·2. $C_{18}H_{20}O_3NBr,C_4H_6O_6$ requires C, 50·0; H, 4·9; Br, 14·2%). The *methiodide*, prepared in ethanol, recrystallised from aqueous ethanol as prisms, m. p. 225°, $[\alpha]_D$ 0·0° (in H_2O) (Found: C, 43·9; H, 4·5; Hal, 39·2. $C_{18}H_{20}O_3NBr,MeI$ requires C, 43·8; H, 4·4; Hal, 39·8%). Degradation of the methiodide in aqueous alkali afforded 1-bromo-β-codeimethine, plates, m. p. 180° (from ethanol) (lit., 182°) $[\alpha]_D$ +193° (2·4% in $CHCl_3$) (Found: C, 57·8; H, 5·9; Br, 20·5. Calc. for $C_{19}H_{22}O_3NBr$: C, 58·1; H, 5·6; Br, 20·4%).

14-*Hydroxycodeinone.*—Thebaine hydrobromide (2 g.), 30% formic acid (10 ml.), and hydrogen peroxide (3 drops; 30%) similarly gave 14-hydroxycodeinone, prisms, m. p. 267° (from ethanol) (lit., 265°) (Found: C, 68·5; H, 6·1; Br, 0·0. Calc. for $C_{18}H_{19}O_4N$: C, 68·9; H, 6·1; Br, 0·0%).

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The Morphine–Thebaine Group of Alkaloids. Part IV. The Structure of the Thebainone Methines and of Thebainone-C.*

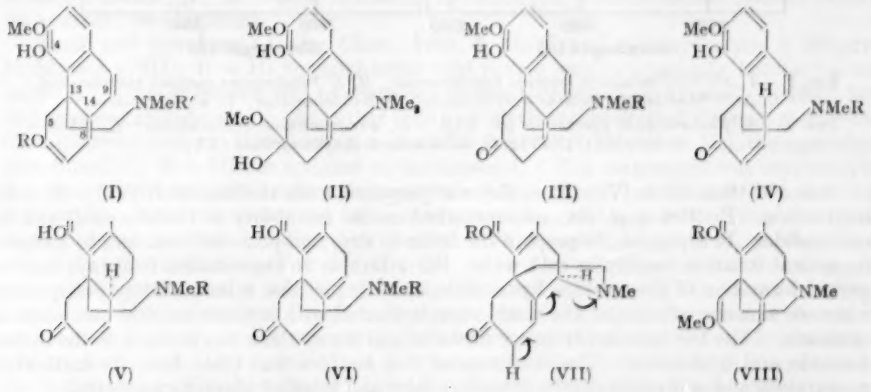
By K. W. Bentley and H. M. E. Cardwell.

[Reprint Order No. 6057.]

The products of hydrolysis of β-dihydrothebaine methine (I; R = R′ = Me) with mineral acid, and of dihydrothebaine-ϕ methiodide (cf. VIII; R = H) with sulphurous acid, originally thought to be the same substance (III; R = Me) (Bentley, Robinson, and Wain, *J.*, 1952, 958) have been shown to be two isomers (III and V; R = Me). A third isomer (VI; R = Me) has been prepared by Hofmann degradation of thebainone-B methiodide. Structures have been allotted to the isomers on the basis of infrared and ultraviolet absorptions. Catalytic hydrogenation of both (III; R = Me) and (V; R = Me) gives β-dihydrothebainone dihydromethine (XII). All three methines are converted into highly coloured substances by aerial oxidation.

The structure allotted by Bentley and Wain (Part I, *J.*, 1952, 967) to thebainone-C has been disproved. This base has been shown to be a cyclic base with the ethanamine chain bridging positions 13 and 8. The steric arrangement of groups at $C_{(14)}$ in thebainone-C has been proved to be the same as in morphine by reduction, degradation, and further reduction to dihydrothebainone dihydromethine.

Although in all other known cases catalytic hydrogenation of substances in the morphine group containing a 8 : 14-double bond leads exclusively to the same steric arrangement at $C_{(14)}$ present in morphine itself, the hydrogenation of thebainone-B methine, hitherto allotted the constitution (III; R = Me), affords β-dihydrothebainone dihydromethine (XII), epimeric at $C_{(14)}$ with the general morphine series (Bentley, Robinson, and Wain, *J.*, 1952, 958). We have investigated this anomaly by preparing the four isomeric thebainone methines (III—VI; R = Me), interconvertible through the common enol (I; R = H, R′ = Me), and we have prepared some of the tautomerides by methods not involving the common enol as an intermediate.



(I) (II) (III) (IV)

(V) (VI) (VII) (VIII)

The $\Delta^{8(14):9}$-methine (III; R = Me) was prepared by mild hydrolysis of β-dihydrothebaine methine (I; R = R′ = Me) (Bentley, Robinson, and Wain, *loc. cit.*) with mineral acid: hydration of the most basic end of the conjugated system leads directly to the hemiketal (II) and thence to the methine (III; R = Me), whose structure was established by the similarity of its ultraviolet absorption to that of β-codeimethine (XVII) and confirmed by the presence of saturated carbonyl stretching bands and the absence of strong C:C bands

* Part III, preceding paper.

characteristic of double bonds conjugated with carbonyl groups in the infrared spectra of the hydriodide and hydrobromide. Ultraviolet extinction curves for the isomeric methines are given in Fig. 1, and optical rotations and infrared data in the Table.

The methines are oxidised so rapidly that optical measurements were made on salts; this precluded infrared solution measurements. Both the hydriodide and the hydrobromide of each tautomeride were prepared by methods that minimised interconversion. The examination of two series of salts was necessary, as in one case the carbonyl band of one salt, but not of both, was sufficiently shifted by polarisation in the crystal for its position not to allow unambiguous decision as to its significance. Optical rotations and ultraviolet absorptions were measured in the presence of sodium dithionite to minimise oxidation.

FIG. 1. FIG. 2.

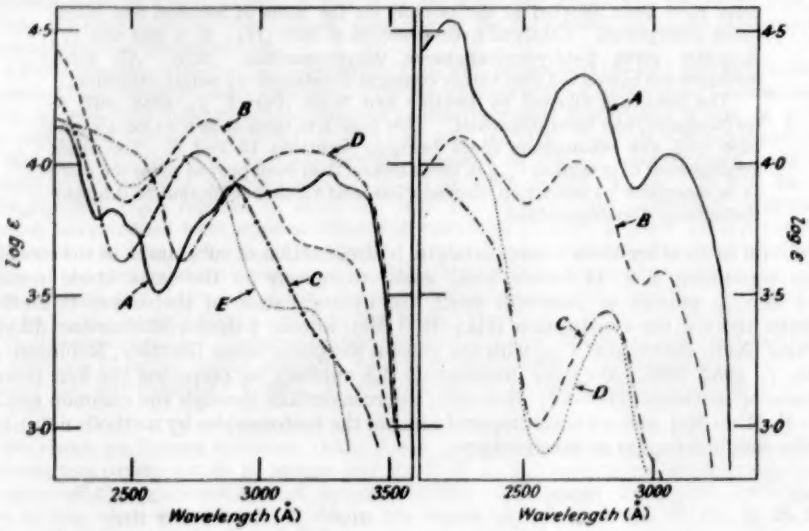


FIG. 1. *A*, $\Delta^{8(14):9}$-*Thebainone methine hydrobromide*; *B*, $\Delta^{7:9}$-*thebainone methine hydrobromide*; *C*, $\Delta^{7:9(14)}$-*thebainone methine hydrobromide*; *D*, *β-codeimethine*; *E*, *α-codeimethine*.

FIG. 2. *A*, *Thebainone-C perchlorate* (cf. XIII); *B*, *α-codeimethine hydrochloride*; *C*, *dihydrothebainone-C* (XIV); *D*, *thebainone-A dihydromethine* (XV).

The $\Delta^{7:9(14)}$-methine (VI; R = Me) was prepared from thebainone-B (VII; R = H) methiodide. Bentley *et al.* (*loc. cit.*) remarked on the instability of thebainone-B and its methiodide. It is possible to prepare the latter in dry, non-polar solvents and to measure its optical rotation rapidly in cold water, but attempts to recrystallise it always lead to partial formation of the methine hydriodide, and the methine is immediately precipitated when an aqueous solution of the methiodide is treated with aqueous sodium carbonate or ammonia. The free base is extremely unstable and the methine was isolated as the hydrobromide and hydriodide. The structure of this methine was clear from its method of preparation and was confirmed by the ultraviolet and infrared absorption spectra.

The hydriodide of the $\Delta^{7:9(14)}$-methine, on treatment with hot sulphurous acid, afforded a different hydriodide, the infrared spectrum of which was distinct from those of the starting material (the $\Delta^{7:9(14)}$-methine) and the $\Delta^{8(14):9}$-methine. Bentley *et al.* (*loc. cit.*) prepared a hydriodide by the action of hot sulphurous acid on the dihydrothebaine-ϕ methiodide. This was presumed, from lack of mixed melting point depression, to be identical with the hydriodide of authentic $\Delta^{8(14):9}$-methine (III; R = Me). However, from its method of preparation it is identical with the new hydriodide prepared from the $\Delta^{7:9(14)}$-methine, and this was confirmed. The infrared and ultraviolet spectra demonstrate that

this substance is the $\Delta^{7:9}$-methine. It was this methine (prepared from dihydrothebaine-ϕ methiodide) that was used in the hydrogenation experiment described by Bentley *et al.*; hence the reductive anomaly was removed as the starting material (V; R = Me) already had the anomalous configuration at $C_{(14)}$. The anomaly returned, however, when we found that the hydrobromide of authentic $\Delta^{8(14):9}$-methine (III; R = Me) on hydrogenation also gave β-dihydrothebainone dihydromethine (XII), but with much less force for our experiments show that (V) is thermodynamically the most stable of the four isomerides. Conversion into the stable isomeride is extremely easy and takes place more rapidly than reduction. Similarly the variability in melting points, which are very sensitive to the rate of heating, and the failure to observe any mixed melting point depressions are probably due to inter-

Diagnostic infrared bands (μ) *and* $[\alpha]_D$ *of thebainone methines.*

Unsaturation	Hydrobromides				Hydriodides			
7 : 9(14)	5·87 [a]	6·01 [c]	6·07 [f]	+ 87°	5·84 [a]	5·97 [c]	6·06 [f]	+ 7·9°
7 : 9	5·83 [a]	5·96 [c]	6·06 [f]	+114	5·90 [a]	6·03 [d]	6·08 [f]	+115
8(14) : 9	5·82 [b]	5·96 [c]		+324	5·82 [b]			+300

[a] Weak bands due to traces of other isomerides or thebainone-B. [b] Saturated ketone group. [c] αβ-Unsaturated ketone group. [d] αβ-Unsaturated ketone group shifted by polarisation in the crystal. [e] αβγδ-Unsaturated ketone group. [f] Double bond conjugated with carbonyl group.

conversion of isomerides. The $\Delta^{8(14):9}$-methine is converted into the $\Delta^{7:9}$-methine by hot sulphurous acid.

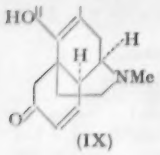
By the severe criterion of carbonyl stretching bands in the infrared spectra each of our products contained *traces* of the other tautomerides, but this does not in any way invalidate our conclusions. More serious was the contamination of the substances (especially the free bases) by coloured oxidation products. This sensitivity precluded lengthy equilibration experiments to determine the relative stability of the various tautomerides.

The methines (III and V; R = Me) appear to form mixed crystals. (We are grateful to Dr. John Robertson, of the Department of Chemical Crystallography in Oxford, who took powder photographs of several preparations. The photographs were very similar and contained many common spacings.) This suggests that in both molecules the three rings are coplanar and further diminishes the remote possibility that the stable tautomeride is the missing methine (IV; R = Me). Although the latter has eluded isolation, indirect proof of its existence was obtained.

Small and Browning (*J. Org. Chem.*, 1939, **3**, 618) found that hydrolysis of dihydrothebaine-ϕ (VIII; R = H) by sulphurous acid gave a sensitive phenolic ketone "α-thebainone." This substance was re-examined by Bentley and Wain (Part I, *J.*, 1952, 967) and renamed thebainone-C. As at that time hydrolysis of dihydrothebainone-ϕ methiodide by sulphurous acid was thought to give the $\Delta^{8(14):9}$-methine (III; R = Me), the equivalent structure (III; R = H) was assigned to thebainone-C. This assignment was supported by the presence of a saturated carbonyl group (infrared spectrum) and the existence of a long-wavelength ultraviolet absorption band of the same $\varepsilon_{max.}$ and $\lambda_{max.}$ as the main absorption band of β-codeimethine (XVII). Our present work, however, suggests the production of one of the other isomerides (V or VI; R = H). The ultraviolet spectrum of thebainone-C, although of much greater intensity than that of α-codeimethine (XVI), shows a striking coincidence of wavelength of the main absorption bands (Fig. 2). The presence of a saturated carbonyl group and a styrenoid chromophore in thebainone-C is only consistent with cyclisation of (III, IV, and V; R = H) at position 8 to give a structural isomeride of the thebainones. This hypothesis has now been established, thebainone-C being the isomeride (XIII) with the usual morphine configuration at position 14.

The structure of thebainone-C was proved by hydrogenation to dihydrothebainone-C (XIV) with uptake of one mol. of hydrogen and disappearance of the styrenoid chromophore (ultraviolet spectrum; Fig. 2). This saturated ketone readily gave a methiodide which was more stable than that of thebainone-B but on treatment with cold aqueous sodium carbonate immediately gave a precipitate of the basic αβ-unsaturated ketone (XV), thebainone-A dihydromethine (Δ^7-dihydrothebainone methine) (CO absorption at 5·97 μ). This on hydrogenation yielded dihydrothebainone dihydromethine (XI).

In the preparation of thebainone-C a colourless crystalline solid separates; this is probably the bisulphite betaine (XVIII) of thebainone-B. On its dissolution in hot water sulphur dioxide is evolved and none of the adduct is recovered. On neutralisation the solution readily becomes coloured through aerial oxidation and thebainone-C slowly crystallises. On careful recrystallisation thebainone-C is obtained as colourless prisms that show none of the characteristic instability of the methines. The sensitivity of thebainone-C commented on by Small and Browning is presumably due to *N*-normethines resulting from the decomposition of thebainone-B.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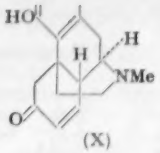
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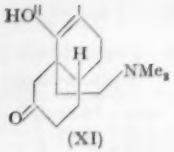
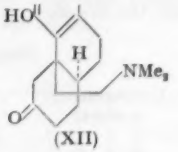

(XI)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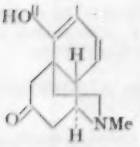
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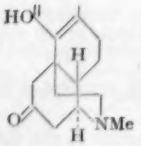
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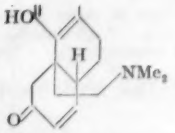
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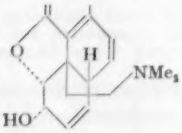

(XVI)

The mode of formation of thebainone-C is now clear. Thebainone-B, first formed by the hydrolysis of dihydrothebaine-ϕ, decomposes to the methine (VI; R = H). If the conditions are not sufficiently vigorous to rearrange this to the more stable (IV and V; R = H), recyclisation takes place by two processes: first, a rapid *trans*-addition of the ethanamine chain and proton, to give β-thebainone-A (IX) and, secondly, by a less rapid, non-stereospecific reaction to give the betaine (XIX) from which thebainone-A (X) is formed by direct transfer of a proton to $C_{(14)}$. If the conditions are more vigorous the methine (VI) is converted into a mixture (IV and V; R = H), these then cyclising at $C_{(8)}$ to give a mixture of thebainone-C and β-thebainone-C, the latter so far having eluded isolation. This mechanism explains our observation that the hydrolysis to thebainone-C is much more reliable if the sulphurous acid treatment is carried out at 40°. The erratic yields (10—30%) of thebainone-C are probably due to the presence of β-thebainone-C [$C_{(14)}$ epimeride of (XIII)]. The formation of β-thebainone-A (IX) in good yield rather than the more stable tautomeride thebainone-A (X) during the treatment of dihydrothebaine-ϕ and thebainone-B with cold aqueous potassium hydrogen sulphate is inexplicable on the basis of the common enol as an intermediate, but is readily explained on the basis of a rapid stereospecific cyclisation.

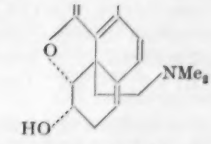
The increasing ease of ring opening in the series thebainone-A, thebainone-C, thebainone-B, parallels the acidity of the enolisable hydrogen atom, which is tertiary in the first case, secondary in the second, and flanked by a carbonyl group and double bond in the last. These observations provide the long-sought degradative evidence for the attachment of the nitrogen atom at $C_{(9)}$ rather than $C_{(10)}$ in the morphine alkaloids.

The immediate liberation of a ring-opened base on treatment of thebainone-B methiodide with aqueous sodium carbonate removes the previously valid argument (Bentley, Robinson, and Wain, *loc. cit.*) that the perchlorate obtained by the brief treatment of the methiodide of dihydrothebaine-ϕ methyl ether (VIII; R = Me) with perchloric acid was the perchlorate of a base. The infrared and ultraviolet spectra have now established that it is the metho-perchlorate of thebainone-B methyl ether (VII; R = Me).

Our experiments suggest that the order of stability of the various tautomeric methines is (V) > (IV) > (III) > (VI). When the nitrogen ring is intact the *cis*-octalone (X) is more stable than the *trans*-octalone (IX) (Gates and Helg, *J. Amer. Chem. Soc.*, **1953**, **75**, 379) and this inversion of the normal order of stability of octalones has been ascribed by Bose (*Chem.*

and Ind., 1954, 130) to interference between the 4-hydroxyl OH group and a hydrogen atom at $C_{(5)}$ in the *trans*-isomer (IX). A similar explanation involving the hydrogen at $C_{(15)}$ may be advanced for the preferential formation of thebainone-C. In the ring-opened isomerides (IV and V; R = Me) there is no longer this radical difference between the two forms, hence the observation that the *trans*-isomeride is the more stable is to be expected and is convincing evidence for the soundness of Bose's ingenious suggestion.

The oxidative instability has precluded any attempt to prepare the missing methine (IV; R = Me) by preparation of the corresponding alcohol followed by oxidation. The colours developed during oxidation are spectacular. The salts in aqueous solution are oxidised even in the presence of sulphurous acid to deep blue and finally black solutions. In non-aqueous solvents the sequence is deep red ⟶ violet ⟶ black. In one case the methiodide of the methine (VI; R = Me) was allowed to oxidise for several weeks, giving a black amorphous solid. This showed a succession of intense absorption bands in the ultraviolet and visible region, extending beyond 6000 Å. It is clearly a mixture, the analysis indicating the addition of up to two atoms of oxygen. The methine (V; R = Me) was oxidised in 2-ethoxyethanol and to aliquot parts of the resulting deep purple solution diluted with ethanol (*a*) sodium dithionite and (*b*) ferric chloride were added until straw-coloured solutions were obtained. These on mixing developed a purple colour. With the methyl ether of (V; R = Me) oxidation also occurs, but the resulting solution is brown, not blue-purple. These preliminary experiments suggest the formation of intermolecular and/or intramolecular quinhydrones, the common enol oxidising at positions 7 and/or 10 and to some extent also in the aromatic ring, giving substances such as (XX), (XXI), and (XXII).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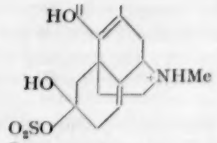
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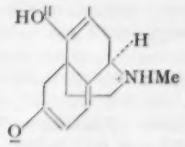
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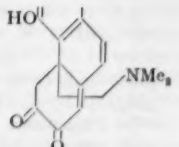
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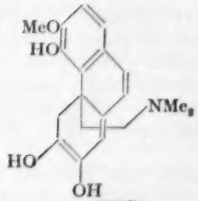
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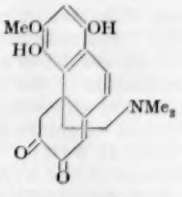
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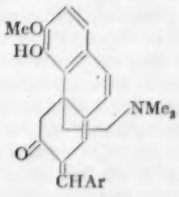
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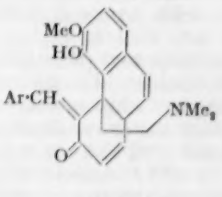
(XXIV)

These changes are doubtless accompanied by some self-coupling as in the decomposition of the sinomenine methines (Goto and Takubo, *Bull. Chem. Soc. Japan*, 1931, **6**, 126). Our observation that the pure piperonylidene derivative (XXIII) of (III; R = Me) is quite stable to aerial oxidation, whilst the piperonylidene derivative prepared by Bentley *et al.* from (V; R = Me), which differed in crystal form from the derivative of (III; R = Me) but gave identical infrared and ultraviolet spectra, was readily oxidised [possibly owing to the presence of traces of 5-piperonylidene derivative (XXIV)], taken together with the fact that marked colour changes on oxidation have not been reported for the sinomenine methines, suggests that a potential CH_2 group at $C_{(7)}$ is essential for the production of the brilliant colours here described. We plan to investigate the oxidation in more detail, the analogy to melanin formation being suggestive.

This work required the preparation of considerable quantities of dihydrothebaine-ϕ. Stork (*J. Amer. Chem. Soc.*, 1952, **74**, 768), contrary to Bentley and Robinson (*Experientia*, 1950, **6**, 353), found it necessary to add ethanol in the reduction of thebaine with sodium

and liquid ammonia, and implied that the ethanol was mechanistically required as a proton source. The rate of reduction of thebaine by sodium and liquid ammonia, without added ethanol, is dependent on the state of subdivision of the thebaine crystals. *Ethanol is never mechanistically required*, but if the crystals are large their rate of solution, and hence the rate of reduction, is increased by the addition of ethanol. When finely divided thebaine (80-mesh sieve) is used, reduction in the absence of ethanol is extremely rapid.

Experimental

Dihydrothebaine-ϕ was prepared by the method of Bentley, Robinson, and Wain (*loc. cit.*). It was advantageous to precipitate the base from alkaline solution by the addition of saturated aqueous ammonium chloride and to extract it *rapidly* with the minimum of quantity of ether. A large quantity of the pure base crystallised from the extract in 45 min. This was collected and a further quantity of slightly less pure material was recovered by concentration of the dried mother-liquors to small bulk. The yield was up to 95%.

The *methobromide* was prepared in toluene (5 parts) at $-20°$ (3 hr.) and recrystallised from water in the presence of sodium dithionite; it was obtained as colourless solvated prisms, m. p. *ca.* 120° with loss of solvent (Found, in material dried at 120°/*in vacuo* : C, 56·5; H, 6·4. $C_{20}H_{24}O_3NBr,H_2O$ requires C, 56·3; H, 6·6%).

Thebainone-B was prepared as the hydrobromide by the hydrolysis of dihydrothebaine-ϕ with alcoholic hydrobromide acid as described by Bentley and Wain (*loc. cit.*). The salt (5 g.) was dissolved in water and shaken with aqueous sodium carbonate and benzene. The organic layer was separated, clarified with anhydrous magnesium sulphate, and treated with methyl iodide, the whole operation being complete within 10 min. After 30 min. the pale yellow flocculent methiodide was collected. (Further quantities of solid separated from the filtrate but were contaminated with methine hydriodide and methiodide.) *Thebainone-B methiodide*, $[\alpha]_D^{18}$ $+21° \pm 8°$ (*c* 1·4 in aqueous sodium dithionite) (Found : C, 52·3; H, 5·8. $C_{18}H_{21}O_3N,CH_3I$ requires C, 51·7; H, 5·8%), could not be recrystallised without the formation of appreciable quantities of $\Delta^{7:9(14)}$-thebainone methine hydriodide; the resulting mixed material, m. p. 200—205° (decomp.), from ethanol was partially solvated (Found : C, 51·0; H, 5·6; N, 2·6. Calc. for $C_{19}H_{24}O_3NI$: C, 51·7; H, 5·8; N, 3·2%).

$\Delta^{8(14):9}$-*Thebainone Methine* (*Thebainone-B Methine*).—β-Dihydrothebaine methine (1 g.) was treated in ethanol (10 ml.) with hydriodic acid (1 ml.). After 10 min. the hydriodide was collected and recrystallised twice from water in the presence of sodium dithionite, forming almost colourless prisms, m. p. 230° (Bentley, Robinson, and Wain give m. p. 214°) (Found : C, 51·6; H, 5·7. Calc. for $C_{19}H_{23}O_3N,HI$: C, 51·8; H, 5·5%). The hydrobromide, prepared similarly, had m. p. 232° (Bentley *et al.* give m. p. 234°). The *piperonylidene derivative* was prepared by the addition of sodium ethoxide to an alcoholic suspension of the hydriodide and piperonaldehyde. After 10 min. the blood-red solution was diluted with water, and the precipitate collected and recrystallised from ethanol; it was obtained as orange felted needles, m. p. 196° (Found : C, 72·8; H, 6·2. $C_{27}H_{27}O_5N$ requires C, 72·8; H, 6·1%).

β-$\Delta^{7:9}$-*Thebainone Methine* (β-*Thebainone-A Methine*).—The hydriodide was prepared as described by Bentley, Robinson, and Wain by the hydrolysis of dihydrothebaine-ϕ methiodide by hot sulphurous acid. The *hydrobromide* was prepared similarly : Dihydrothebaine-ϕ methobromide (4 g.) was dissolved in boiling water (25 ml.) and sulphur dioxide passed through the solution for 10 min., during which it became dark blue. The solution was rapidly evaporated to dryness. The residue recrystallised from ethanol in presence of sodium dithionite as colourless prisms, m. p. 235°, $[\alpha]_D^{20}$ +114° (*c* 1·8 in EtOH) (Found : C, 57·5; H, 6·0. $C_{19}H_{23}O_3N,HBr$ requires C, 57·9; H, 6·1%).

$\Delta^{7:9(14)}$-*Thebainone Methine*.—Thebainone-B methiodide (5 g.), dissolved in cold aqueous sodium dithionite (20 ml.), was treated with aqueous sodium carbonate. The white precipitate, which separated immediately, was rapidly collected and transferred at once into aqueous hydrobromic acid containing sodium dithionite (the base began to become brown in air even with the most rapid manipulation). On trituration hydrated $\Delta^{7:9(14)}$-*thebainone methine hydrobromide* separated. This crystallised from ethanol–ether in pale pink needles, m. p. 217—223° (decomp.) alone or when mixed with the $\Delta^{8(14):9}$-methine hydrobromide (Found : C, 55·4; H, 6·2. $C_{19}H_{23}O_3N,HBr,H_2O$ requires C, 55·3; H, 6·3%). It had $[\alpha]_D^{18}$ $+87° \pm 14°$ (in aqueous sodium dithionite). The aqueous filtrate from the hydrobromide was poured into saturated aqueous potassium iodide. The crystals that separated were then collected and recrystallised from ethanol–ether; $\Delta^{7:9(14)}$-*thebainone methine hydriodide* was obtained as blue needles, m. p.

221—226°, $[\alpha]_D^{18}$ +79° ± 30° (in aqueous sodium dithionite) (Found: C, 51·5; H, 5·3. $C_{19}H_{22}O_3N,HI$ requires C, 51·7; H, 5·4%).

Conversion of $\Delta^{7:9(14)}$*-Thebainone Methine into the* $\Delta^{7:9}$*-Methine.*—$\Delta^{7:9(14)}$-Thebainone methine hydriodide was dissolved in hot water through which a stream of sulphur dioxide was continuously bubbled for 20 min. on the water-bath. The mixture was then heated to expel this gas. On cooling, the deep blue solution deposited the $\Delta^{7:9}$-methine hydriodide, which formed prisms, m. p. 215—225°, from water. As the isomeric methines cannot be differentiated by m. p. this salt was identified as the $\Delta^{7:9}$-methine hydriodide by its infrared spectrum in a paraffin mull.

Reduction of $\Delta^{8(14):9}$*-Thebainone Methine* (*Thebainone-B Methine*).—$\Delta^{8(14):9}$-Thebainone methine hydrobromide (1 g.) in water (35 ml.) was shaken under hydrogen in presence of platinum oxide (60 mg.) until absorption of hydrogen ceased (2·05 mols.). The catalyst was removed, and the base precipitated with sodium carbonate, washed, and recrystallised from 50% ethanol; β-dihydrothebainone dihydromethine was obtained as almost colourless needles, m. p. and mixed m. p. 179° (Small and Browning, *loc. cit.*, give m. p. 177—179°; Bentley, Robinson, and Wain, *loc. cit.*, m. p. 179°).

Oxidation of Methines.—(*a*) $\Delta^{7:9(14)}$-Thebainone methine hydrobromide was shaken with aqueous sodium carbonate and ether, the ether layer separated, dried ($MgSO_4$), diluted with ethanol and treated with methyl iodide. The solution was then left for 2 months exposed to air. The solution became red, then violet, and finally deposited a black semicrystalline substance. This *substance* was dissolved in ethanol and partially reprecipitated on addition of ether (Found: C, 49·1; H, 5·5; I, 24·1. $C_{20}H_{24}O_5NI$ requires C, 49·5; H, 5·0; I, 26·2%). In water a deep purple solution was obtained, which was immediately decolorised on addition of aqueous sodium dithionite, ferric chloride, or chromic acid.

(*b*) $\Delta^{7:9}$-Thebainone methine (1 g.) was dissolved in 2-ethoxyethanol (5 ml.) and air bubbled rapidly through the solution for 24 hr., during which the solution became very deep purple. Equal portions were diluted with ethanol until the depth of colour was considerably reduced. One portion was then treated with aqueous sodium dithionite, and the other with warm alcoholic ferric chloride until the colour was just discharged. The two solutions were then mixed; a purple solution was obtained.

Thebainone-C.—This was prepared by a modification of Small and Browning's method (*loc. cit.*). Dihydrothebaine (5 g.) was dissolved in water (75 ml.) saturated with sulphur dioxide and the solution set aside at 40° for 1 hr. In all experiments after the fourth, a colourless crystalline *compound* separated after 10—15 min. When separated this was found to be very sparingly soluble in cold water but readily soluble in hot water, though it could not be recovered by cooling the solution [Found: C, 52·5; H, 6·5. $C_{18}H_{23}O_6NS,2H_2O$ (*i.e.*, XVIII) requires C, 53·0; H, 6·6%]. The yield of thebainone-C was not noticeably affected whether the solid alone or the whole reaction mixture was worked up. The mixture was neutralised with ammonia in the presence of sodium dithionite, the precipitated gummy base was extracted with ether, and the extracts were washed with water and decanted from gum, dried, and evaporated under hydrogen. The residue was dissolved in alcohol (6 ml.), and water containing a small amount of sodium dithionite was added to the resulting dark brown solution (which then became pale yellow) until precipitation of a yellow oil just began. A few drops of alcohol were then added and the mixture set aside under hydrogen for one week during which colourless prisms separated together with some brown resinous material. Crystallisation was much more rapid if methanol containing two drops of aqueous sodium dithionite was used instead of aqueous ethanol at this stage. Of sixteen experiments carried out at 40° none was unsuccessful. Thebainone-C so obtained was washed with methanol (which removed the resinous material) and recrystallised from methanol. The first recrystallisation removed most of the impurities and the mother-liquors quickly became dark violet. A second recrystallisation yielded thebainone-C as colourless prisms, m. p. 190° (Small and Browning, *loc. cit.*, give m. p. 185—186°; Bentley and Wain, *J.*, 1952, 967, m. p. 186—187°), stable in air. The perchlorate was obtained as colourless leaflets, m. p. 201° (Bentley and Wain give m. p. 200°); the *picrate* was prepared in ethanol and recrystallised from 2-ethoxyethanol as canary-yellow plates, m. p. 186° (decomp.), darkening in strong sunlight (Found: C, 54·6; H, 4·4; N, 10·1. $C_{24}H_{24}O_{10}N_4$ requires C, 54·5; H, 4·55; N, 10·6%).

Dihydrothebainone-C.—Thebainone-C (550 mg.) was shaken in glacial acetic acid (15 ml.) under hydrogen in the presence of platinum oxide (60 mg.) until absorption of hydrogen ceased (0·98 mol.). The solution was filtered, the acetic acid removed by distillation *in vacuo*, the residue dissolved in water, and the base precipitated with ammonia, washed with water, and dried. It was dissolved in hot 1 : 1 benzene–light petroleum (b. p. 80—100°), but crystallisation did not occur until water was added or was absorbed from the atmosphere. A hemihydrate of

dihydrothebainone-C then separated as colourless prisms, m. p. 143°, $[\alpha]_D^{20}$ −70° (*c* 2·0 in $CHCl_3$) (Found: C, 69·3; H, 7·6. $C_{18}H_{23}O_3N,\frac{1}{2}H_2O$ requires C, 69·6; H, 7·7%). Anhydrous material did not crystallise. (Thebainone-A behaves in the same way; Gates and Helg, *J. Amer. Chem. Soc.*, 1953, **75**, 380, footnote 2.) The base is readily soluble in organic solvents except petroleum, and in ethanol gives a blue colour with ferric chloride. The *perchlorate*, prepared in ethanol, crystallised from 95% ethanol as colourless elongated prisms, m. p. 260° (decomp.) (Found: C, 54·0; H, 5·9; Cl, 8·8. $C_{18}H_{23}O_3N,HClO_4$ requires C, 53·8; H, 6·0; Cl, 8·8%). The *picrate*, prepared in ethanol, crystallised from aqueous 2-ethoxyethanol as canary yellow plates, m. p. 205—206°, darkening in strong sunlight (Found: C, 54·3; H, 4·8; N, 10·3. $C_{24}H_{26}O_{10}N_4$ requires C, 54·3; H, 4·9; N, 10·5%).

Thebainone-A Dihydromethine (Δ^7-*Dihydrothebainone Methine*) (XV).—Dihydrothebainone-C (4 g.) was dissolved in benzene (20 ml.), and methyl iodide (5 ml.) added. After 3 hr. the methiodide was collected and dissolved in water (55 ml.). Adding 10% aqueous sodium carbonate (15 ml.) produced an immediate precipitate. This was extracted with hot benzene and the extract allowed to cool. Colourless needles which separated recrystallised from benzene, giving *thebainone-A dihydromethine* (Δ^7-*dihydrothebainone methine*) as felted colourless elongated needles, m. p. 153·5°, $[\alpha]_D^{20}$ +40° (*c* 1·9 in $CHCl_3$) (Found: C, 72·1; H, 8·2. $C_{19}H_{25}O_3N$ requires C, 72·4; H, 7·9%); there was a carbonyl absorption band at 5·97 μ. The *methoperchlorate* was obtained as colourless prisms, m. p. 234°, from water containing 5% of ethanol (Found: C, 55·5; H, 6·3. $C_{20}H_{28}O_7NCl$ requires C, 55·8; H, 6·5%).

Reduction of Thebainone-A Dihydromethine.—The methine (1·5 g.) in glacial acetic acid (50 ml.) was shaken under hydrogen in presence of platinum oxide (60 mg.) until absorption of hydrogen ceased (0·97 mol.). The catalyst and solvent were removed, the residue dissolved in water, and ammonia added. The precipitated base was washed with water and recrystallised from 25% ethanol, giving dihydrothebainone dihydromethine as colourless needles, m. p. 138°. The picrate was obtained as rosettes of yellow needles, m. p. 185—186°, from aqueous 2-ethoxyethanol (lit., m. p. 185—187°). The methiodide was converted into thebenone by Wieland and Kotake's method (*loc. cit.*) and the product obtained as colourless needles, m. p. and mixed m. p. 136° (lit., m. p. 136°).

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The Morphine–Thebaine Group of Alkaloids. Part V. The Absolute Stereochemistry of the Morphine, Benzylisoquinoline, Aporphine, and Tetrahydroberberine Alkaloids.*

By K. W. Bentley and H. M. E. Cardwell.

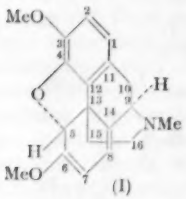
[Reprint Order No. 6058.]

The absolute stereochemistry of the various asymmetric centres in the morphine alkaloids has been deduced. The change of optical rotation with polarity of solvents is of the same type in the benzyl*iso*quinoline and the tetrahydroberberine alkaloid series but there is an inversion in the aporphine alkaloids. The benzyl*iso*quinoline, aporphine, and tetrahydroberberine alkaloids that accompany the morphine and sinomenine alkaloids in Nature are enantiomorphous with the latter.

With the syntheses of morphine (Gates and Tschudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1109; Elad and Ginsburg, *ibid.*, 1954, **76**, 312) Gulland and Robinson's formula for morphine (*J.*, 1923, 980; *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, **69**, 79) received final confirmation. These syntheses did not, however, establish the stereochemical arrangement of the various asymmetric centres. The stereochemistry of the morphine alkaloids was first discussed by Schöpf (*Annalen*, 1927, **452**, 211) who suggested that the nitrogen-containing ring was *trans* to the oxide ring as in (I). His argument was influenced by the observation (Freund and Speyer, *J. prakt. Chem.*, 1916, **94**, 135; Schöpf and Borkowsky, *Annalen*, 1927, **452**,

* Part IV, preceding paper.

249) that 14-hydroxydihydrocodeinone methine (II) on Hofmann degradation gave a cyclic ether " dihydrohydroxycodeone " (III). The *cis*-relationship of the 14-hydroxy-group and the ethanamine chain was thus established, but there was no unequivocal evidence that the hydroxyl group in 14-hydroxycodeinone had the same steric arrangement as the hydrogen atom at $C_{(14)}$ in morphine and codeine. The vital nature of this missing link becomes apparent when the stereochemistry of dihydrocodeinone is considered (see below). Lutz and Small (*J. Org. Chem.*, 1939, **4**, 220) provided evidence that strongly suggested, but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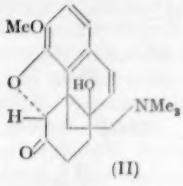
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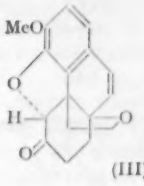
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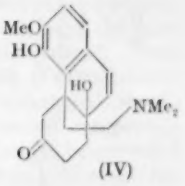
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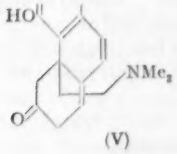
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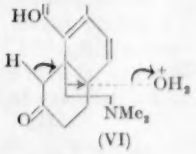
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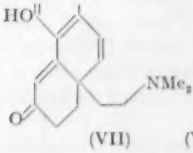
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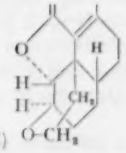
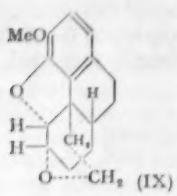

(VIII)

did not prove, that $C_{(14)}$ has the same stereochemistry in these compounds. We have noticed, however, one unexplained reaction in the literature that may be relevant to this problem.

Schöpf and Borkowsky (*loc. cit.*) reported that the methine (IV), unlike other 14-hydroxy-compounds, is readily dehydrated by warm hydrobromic acid to a substance formulated as (V), but the hydrobromide so produced is quite different from that of the authentic methine (V) (Bentley, Robinson, and Wain, *J.*, 1952, 958) and from the other tautomerides described by us (preceding paper). Indeed, from its reported resistance to aerial oxidation it cannot possibly be any of the thebainone methines and must accordingly be a rearrangement product. If the OH group is *trans* to the ethanamine chain (cf. VI), this could be most readily viewed as a concerted dehydration and rearrangement to metathebainone methine (VII). We have found that the hydrobromide of (VII) corresponds exactly with that obtained by Schöpf, particularly in crystallising with a fractional molecule of water that cannot be removed in *vacuo* at 120°. However, non-stereospecific dehydrations with rearrangement are known (cf. the conversion of borneol and *iso*borneol into camphene by 50% sulphuric acid; Konowalov, *J. Russ. Phys. Chem.*, 1900, **32**, 76; Gobulov, *ibid.*, 1912, **44**, 1061), and any thought that this rearrangement allows a distinction in favour of (VI) rather than (IV) was dispelled by the fact that dissolution of any of the thebainone methines in 40% hydrobromic acid and subsequent treatment with aqueous sodium hydroxide afforded the deep yellow colour characteristic of metathebainone derivatives in alkali. This, however, is not a preparative method for metathebainone methine.

This illustrates the ambiguity attached to all chemical attempts to probe the stereochemistry of the morphine alkaloids. This was recognised by Rapoport and Lavigne (*J. Amer. Chem. Soc.*, 1953, **75**, 5329) in their degradations of the isomeric thebenones, but the ambiguity is also present in the work of Rapoport and Payne (*ibid.*, 1952, **74**, 2630) who found that exhaustive methylation of dihydro*iso*codeine affords 2% of a product, codiran (VIII), in which the residue of the ethanamine chain has cyclised with the 6-hydroxyl group. Together with the previous proof (Rapoport and Payne, *J. Org. Chem.*, 1950, **15**, 1093) of the *trans*-relation of the 5- and the 6-oxygen atom in dihydro*iso*codeine this led to a *trans*-arrangement of the oxide and nitrogen rings in codeine. A study of models reveals the ambiguity, for the cyclic product (VIII) is highly strained, whilst a strainless model of the isomeride (IX) can be constructed. Thus the very low yield of codiran could

be due either to the difficulty of formation of the strained product (VIII) or to an abnormal reaction in which $-NMe_3^+$ is replaced by –OH and the resulting ethanol chain performs a substitution by inversion at $C_{(6)}$ leading to the strain-free form (IX).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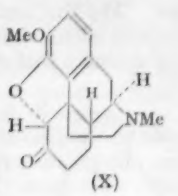
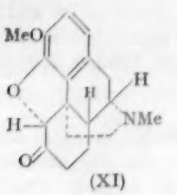

(X)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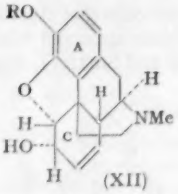
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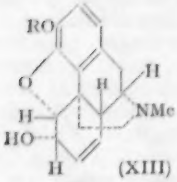
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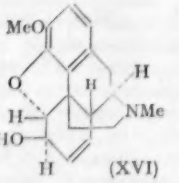
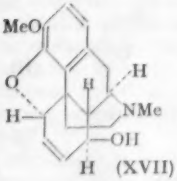

(XVI)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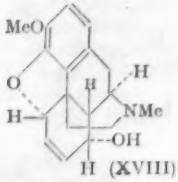
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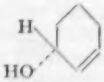
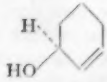

(XIV)


(XV)

In view of these ambiguities we investigated the stereochemistry by physical methods. Only two stereochemical arrangements, (X) and (XI) (or their mirror images), need be considered for (−)-dihydrocodeinone [which is known to have the same stereochemistry at $C_{(14)}$ as morphine and is not epimerised at $C_{(5)}$ by alkali (Schöpf, *loc. cit.*)], as a study of models shows that inversion at $C_{(5)}$ [or, of course, at $C_{(14)}$] in (X) or (XI) leads to a highly strained oxide ring. This disposes of Stork's attempt ("The Alkaloids," Academic Press Inc., New York, 1952, Vol. II, 171) to deduce the stereochemistry of morphine without reference to Schöpf and Borkowsky's work on 14-hydroxycodeinone. If the hydroxyl group in 14-hydroxydihydrocodeinone has the same configuration as the $C_{(14)}$ hydrogen atom in dihydrocodeinone then the latter must be (X); if this is not established then there are no *a priori* grounds for rejecting (XI). Stork's subsequent attempt (*op. cit.*, p. 190) to deduce a *trans*-relation of the oxide ring and ethanamine chain as in (X) by postulating a concerted *trans*-elimination mechanism in reactions leading to acetylmethylmorphol is equally unsatisfactory, for to maintain this argument he subsequently (*op. cit.*, p. 191) overlooks the fact that the Hofmann degradation of α- and β-codeimethine to methylmorphenol involves a *cis*-elimination of the ethanamine chain and the hydrogen atom from position 5.

Structures (X) and (XI) for dihydrocodeinone may be expanded to (XII and XIII; R = H) respectively for (−)-morphine. The former was derived from Schöpf's expression for thebaine (I) by Fieser and Fieser ("Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 23) and is supported by the work of Rapoport and his co-workers (*loc. cit.*); the latter formula is, however, not excluded by the chemical evidence.

At our suggestion Mrs. D. M. Crowfoot-Hodgkin and Mrs. M. Mackay very kindly undertook an *X*-ray investigation, and their proof that (−)-morphine is (XII) or its mirror image, and not (XIII) (R = H), is given in the following paper. We, however, probed the relative stereochemistry by determining the absolute stereochemistry at as many centres as possible: our results established that (−)-morphine is (XII; R = H) and not the enantiomorph.

Absolute Stereochemistry at $C_{(5)}$.—Mills (*J.*, 1952, 4976) has shown that, in the terpene series, allylic alcohols containing the *cyclo*hexenol structure (XIV) are less lævorotatory than those containing the epimeric structure (XV). This method was successfully extended

to the steroids and, assuming that the same arguments may be applied to semi-boat rings (see below), we have now used it with success in the morphine series. Codeine (XII; R = Me), $[\alpha]_D$ −112° ($CHCl_3$), is less lævorotatory than *iso*codeine (XVI), $[\alpha]_D$ −151° ($CHCl_3$); and *ψ*-codeine (XVII), $[\alpha]_D$ −97° (EtOH), is less lævorotatory than *allo*-*ψ*-codeine (XVIII), $[\alpha]_D$ −235° (EtOH); this suggests that these bases have the absolute stereochemistry shown in the formulæ. This argument assumes that the hydroxyl groups in codeine and *allo*-*ψ*-codeine are *cis* to the 5-oxygen atom. This is certainly true for codeine (Rapoport and Payne, *loc. cit.*) and the orientation in other cases may be deduced. Ring C is roughly coplanar with the nitrogen ring in (XII) and with ring B in (XIII). In both cases, hydroxyl groups of the same orientation with reference to the oxide ring or $C_{(14)}$ will have the same conformation (axial or equatorial) with reference to the coplanar bicyclic systems. Compounds derived by sodium and alcohol reduction of $C_{(6)}$- and $C_{(8)}$-ketones (*α*-*iso*morphine, *iso*codeine, dihydrothebainol-A, *γ*-*iso*morphine, *ψ*-codeine, dihydro-*ψ*-codeine-A) should have equatorial hydroxyl groups (Barton, *J.*, 1953, 1027). The epimeric compounds (morphine, codeine, dihydrothebainol-B, β-*iso*morphine, *allo*-*ψ*-codeine) might be expected to have axial hydroxyl groups and this is almost certainly true for compounds in which the oxide ring is broken. In morphine, however, the 6-hydroxyl group can become equatorial with reference to the planar bicyclic system if ring C has a semi-boat rather than a semi-chair configuration, and the *X*-ray analysis (see following paper) shows that morphine does have a semi-boat ring C. Thus in so far as *iso*codeine is more stable than codeine this is due to a change of ring C from a boat to a chair configuration rather than a change in orientation of the 6-hydroxyl group.

Absolute Stereochemistry at $C_{(13)}$ *and* $C_{(14)}$.—The nitrogen-containing ring must be *cis*-fused to the hydrophenanthrene system; hence determination of the absolute stereochemistry at either $C_{(13)}$ or $C_{(9)}$ allows a distinction between (XII) and (XIII). Bick (*Nature*, 1952, **169**, 756) pointed out that the rearrangement of morphine to *apo*morphine (XIX) leaves only one asymmetric centre. In principle Leithe's extension (*Ber.*, 1930, **63**, 1498) of Clough's method (*J.*, 1918, **113**, 526) may be used to determine the absolute stereochemistry of the latter base. Bick reported that the rotations of *apo*codeine and *apo*morphine became less lævorotatory as the solvent polarity increased and on this basis assigned to *apo*morphine and hence to morphine an absolute stereochemistry at $C_{(9)}$ that, with our determination at $C_{(6)}$, leads to (XIII; R = H) for morphine. If this were correct then rings A, B, and C would be coplanar and there would be an enantiomorphous resemblance between rings C and B of the morphine alkaloids and rings A and B of the steroids. We therefore compared the rotations of cholestane (XX) and 2- and 4-oxygenated cholestanes with those

TABLE 1.

Cholestane derivative	$[\alpha]_D$	Δ	Alkaloid	$[\alpha]_D$	Δ
Cholestane [1]	+24·5°	—	Tetrahydrodeoxycodeine (XXII)	−34°	—
-2β-ol [2]	+33	+ 8·5°	Dihydrothebainol-B (XXV)	−36·5	− 2·5°
-2α-ol [2]	+36	+11·5	Dihydrothebainol-A (XXVI)	−46·2	−12·2
-2-one [2]	+49	+24·5	Dihydrothebainone (XXVII)	−80	−46
-4β-ol [3]	+29·9	+ 5·4	Tetrahydro*allo*-*ψ*-codeine (XXVIII)	−58	−24
-4α-ol [4]	+ 2·8	−21·7	Tetrahydro-*ψ*-codeine (XXIX)	−17·8	+16·2
-4-one [2]	+29·5	+ 5·0	Tetrahydro-*ψ*-codeinone (XXX)	+ 8·0	+42

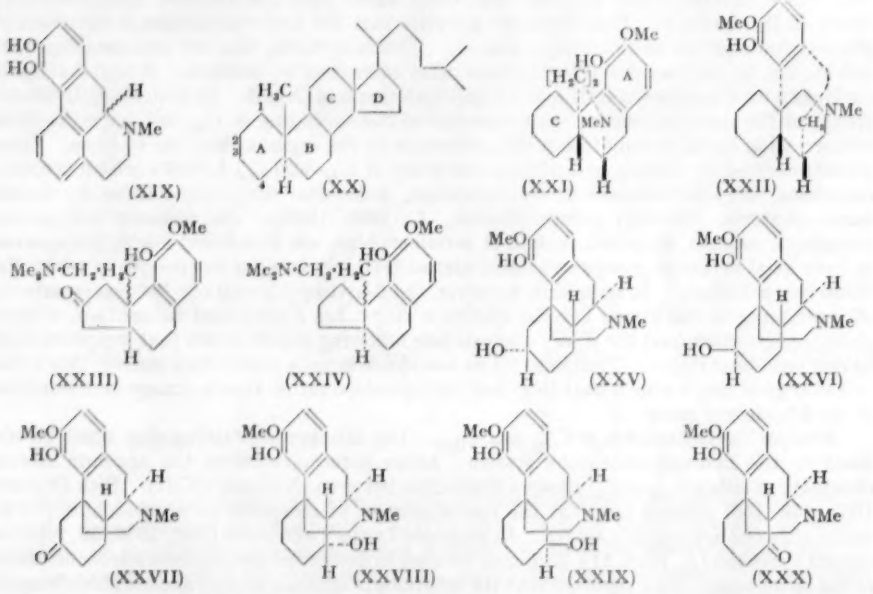
Steroid rotations in chloroform, alkaloid rotations in ethanol.

[1] Stavely and Bergmann *J. Org. Chem.*, 1937, **1**, 567. [2] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 524, 727. [3] Furst and Scotoni, *ibid.*, 1953, **36**, 1382. [4] Plattner, Petrzilka, and Lang, *ibid.*, 1944, **27**, 513.

Alkaloid references: see Bentley, "The Chemistry of the Morphine Alkaloids," The Clarendon Press, Oxford, 1954.

of tetrahydrodeoxycodeine (XXI on the basis of XIII for morphine) and its oxygenated derivatives. The results are given in Table 1; with one exception the introduction of functional groups produces changes of rotation of opposite sign to the corresponding changes in the cholestane series, the one exception occurring when a polarisable group (CO) is near to the asymmetric centre ($C_{(9)}$) that is not present in the steroids. We thus have strong evidence that the morphine alkaloids are enantiomorphous to the steroids, but

further examination reveals that this condition is also met by (XII); thus in (XXII) it is the hydrogenated *iso*quinoline system that is largely coplanar, the benzene ring being the angular substituent. Thus the parallelism shown in Table 1 establishes the absolute stereochemistry at $C_{(14)}$ but not that at $C_{(13)}$.



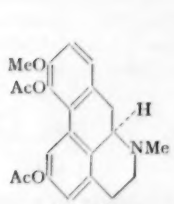
When the nitrogen ring is broken a further test should be possible, but in the absence of relevant optical data for the required pairs of compounds it is necessary to contract ring C in the alkaloids before a test can be made. In the sinomenine series (enantiomorphous with morphine) dihydrosinomenilone dihydromethine (XXIII), $[\alpha]_D$ −24·6° ($CHCl_3$) (Goto and Takubo, *Annalen*, 1932, **499**, 169), is much more lævorotatory than dihydrosinomenilan dihydromethine (XXIV), $[\alpha]_D$ +45·6° (Goto and Shishido, *ibid.*, 1933, **507**, 296). In the steroids A : B-*trans*-indanones have far more positive rotations than the corresponding indanes; hence sinomenilone derivatives cannot have the ethanamine chain *trans* to the hydrogen at $C_{(14)}$, and sinomenine methines must be of the coprostane type and morphine methines must be enantiomorphous with coprostane and not with cholestane. We thus provisionally conclude that morphine must be (XII).

TABLE 2. *Specific rotations in various solvents.*

Substance	CS_2	*cyclo*-Hexane	Benzene	Pyridine	$CHCl_3$	EtOH	Base in N-HCl or hydrochloride in H_2O
(−)-Phenylethylamine [3]	—	−42·6°	—	—	−35·2°	−30·4°	−5·4°
(−)-*N*-Ethyl-1-phenylethylamine [3]	—	—	—	—	—	−53·2	−12·2
(−)-Tetahydro-*N*-methyl*iso*quinoline [3]	—	−79·9	—	—	−71·6	−71·5	−34·0
1-Benzyltetrahydro-*N*-methyl-*iso*quinoline [3]	−65·8°	−46·8	−35·3°	−25·2°	+30·0	+64·0	+72·0
(+)-Laudanosine [1]	− 8·0	—	+ 2·2	+ 8·3	+52	+90	+102
(−)-Diacetylmorphothebaine [4]	−173	—	−92	−106	−82	−66	−39
(−)-Tetrahydroprotoberberine [3]	—	−462	—	—	−386	−377	−255
(+)-Glaucine [4]	+115	+125	—	+99	+138	+120	+110

[1] Leithe, *Ber.*, 1930, **63**, 1498. [3] *Idem*, *ibid.*, p. 2343. [3] *Idem*, *Ber.*, 1931, **64**, 2827. [4] This paper.

Absolute Stereochemistry at $C_{(9)}$.—Bick's allocation of absolute stereochemistry at $C_{(9)}$ now requires re-examination. The possibility that the rotatory changes of *apo*morphine and *apo*codeine were due to variations in phenolic betaine concentration with solvent polarity was excluded by the examination of diacetylmorphothebaine (XXXI). This base showed an increase in lævorotation with increasing solvent polarity (Table 2), and, in agreement with



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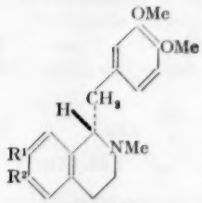
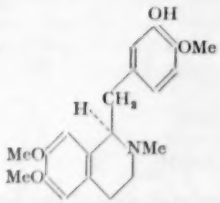
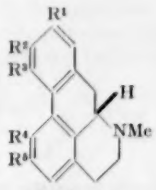


(XXXII)



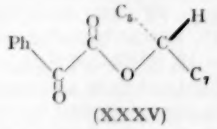
(XXXIII)



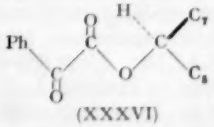
(XXXIV)

Bick's conclusion, appears to have the same absolute stereochemistry as (+)-laudanosine (XXXII; $R^1 = R^2 = Me$), which has been related (see Table 2) to (−)-1-phenylethylamine and thence by oxidation to (+)-alanine (Leithe, *Ber.*, 1930, **63**, 2343; 1931, **64**, 2827). This relation can be tested, as Faltis and Adler (*Arch. Pharm.*, 1951, **284**, 281) have prepared (−)-glaucine from (−)-laudanosine. (+)-Glaucine (XXXIV; $R^3 = H$, $R^1 = R^2 = R^4 = R^5 = OMe$) should therefore, if Bick is correct, show a similar variation of rotation with solvent polarity to (−)-diacetylmorphothebaine. For the three most polar solvents (+)-glaucine (we are grateful to Dr. R. H. F. Manske for the gift of a sample) shows the opposite variation, and therefore belongs to the opposite series from (−)-diacetylmorphothebaine, which must accordingly be (XXXI) and morphine must be (XII; R = H).

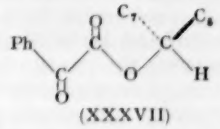
This conclusion can be put to the test. The absolute stereochemistry at $C_{(6)}$ is satisfactorily established by interlocking optical evidence. The weakest link is the evidence on the absolute stereochemistry at $C_{(9)}$. Application of Prelog's method (*Helv. Chim. Acta*, 1953, **36**, 308) to the optical rotation of the atrolactic acid resulting from the treatment of the phenylglyoxylyl ester of dihydrocodeine with methylmagnesium iodide, paradoxically gives no information about the absolute stereochemistry at $C_{(6)}$, but if the stereochemistry at this centre is regarded as settled the result does allow a distinction between (XII and XIII; R = H) for morphine. The three conformations of the phenylglyoxylate are (XXXV), (XXXVI), and (XXXVII) the groups in order of size being $C_{(5)} > C_{(7)} > H$. If dihydrocodeine were as (XIII, 7 : 8-dihydro; R = Me) then, as shown by models, as in the cases studied by Prelog, attack by the Grignard reagent on conformation (XXXV) would be from above and on conformations (XXXVI) and (XXXVII) from below, leading, on



(XXXV)



(XXXVI)

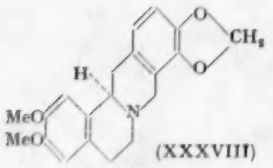


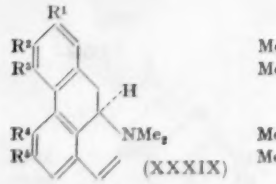
(XXXVII)

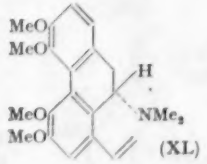
hydrolysis, to an excess of (+)-atrolactic acid. However, models show that the conformation (XXXVII) is impossible with the structure (XII, 7 : 8-dihydro; R = Me) for dihydrocodeine, and that moreover in conformation (XXXI) attack from below is seriously hindered by the 3-methoxyl group, so that attack from above will be accentuated and will more than compensate for the slightly preferred attack from below shown by configuration (XXXVI). Thus an excess of (−)-atrolactic acid should be obtained on hydrolysis. The atrolactic acid isolated from this sequence of reactions had $[\alpha]_D^{18}$ −5·73°, thus confirming the structure (XII; R = H) for morphine. The arrangement of groups deduced by Schöpf, by Fieser and Fieser, by Rapoport and his co-workers (*loc. cit.*), and by Bose (*Chem. and Ind.*, 1954, 130) is thus confirmed.

The ambiguity observed earlier in the optical comparison of steroids and hydrogenated

codeine derivatives and the observation that benzyl*iso*quinolines and aporphine alkaloids have the same stereochemistry when their rotatory variations with solvent polarity are opposite, illustrate a principle that is sometimes neglected. In comparisons of optical data the spatial arrangements of the molecules must be studied. Thus, in the benzyl*iso*quinolines the preferred conformation will be that (XXXIII) in which the benzene nucleus is


(XXXVIII)


(XXXIX)

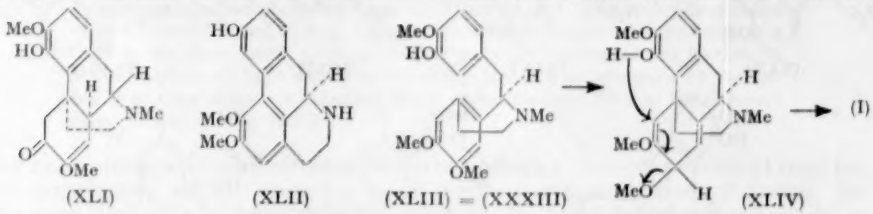

(XL)

remote from the unsaturated ring of the tetrahydro*iso*quinoline. Cyclisation to a tetrahydroberberine (XXXVIII) then involves little geometrical change. In conformity with this, Leithe (*Ber.*, **1934**, **67**, 1261) has prepared (−)-tetrahydroprotoberberine (deoxy-XXXVIII) from (−)-benzyltetrahydro*iso*quinoline and has shown that in these two compounds the optical rotation changes with solvent polarity in the same manner. Cyclisation to an aporphine, however, involves a major change of shape, hence it is not surprising that the dependence of rotation on solvent polarity also changes.

The proof that (+)-glaucine and (−)-morphothebaine are enantiomorphous suggests the assignment of all aporphine alkaloids that are dextrorotatory in ethanol or chloroform to the (−)-1-phenylethylamine series. All the 2 : 3 : 5 : 6-tetra-oxyaporphines [(+)-domesticine, (+)-dicentrine, (+)-laurotetanine, (+)-actinodaphnine, and (+)-boldine] that have been related to (+)-glaucine are represented by (XXXIV; R^3 = H, R^1, R^2, R^4, R^5 = OX) (for references see Henry, " The Plant Alkaloids," 4th Edn., Churchill, 1949). None of the 3 : 4 : 5 : 6-tetra-oxyaporphines has been related to the glaucine series, but in addition to the sign of rotation, which assigns to (+)-bulbocapnine, (+)-corydine, (+)-*iso*-corydine (artabotrinine), (+)-corytuberine, and (+)-suaveoline the structure (XXXIV) we note that aporphine alkaloids on Hofmann degradation give *iso*methines of opposite sign of rotation to the parent base. Thus *apo*morphine dimethyl ether, $[\alpha]_D$ −148°, gives an *iso*methine (XXXIX; $R^1 = R^4 = R^5$ = H, $R^2 = R^3$ = OMe), $[\alpha]_D$ +139°. *iso*Corydine methyl ether (XXXIV; R^1 = H, $R^2 = R^3 = R^4 = R^5$ = OMe), $[\alpha]_D$ +182°, gives an *iso*methine (XL), $[\alpha]_D$ −183°, and this confirms our assignment of the dextrorotatory aporphines to a series enantiomorphous to (−)-morphothebaine. In the trioxyaporphines, *iso*thebaine methyl ether, $[\alpha]_D$ +235°, gives an *iso*methine, $[\alpha]_D$ −284° (Klee, *Arch. Pharm.*, **1914**, **252**, 211); hence despite the fact that the position of the oxygen atoms has not been clearly established we can assign *iso*thebaine to the series (XXXIV). In the dioxyaporphines, (−)-roemerine (5 : 6-methylenedioxyaporphine), $[\alpha]_D$ −77°, on demethylation, methylation, and degradation affords an *iso*methine, $[\alpha]_D$ +14°; we can therefore assign to (+)-roemerine the constitution (XXXIV; $R^1 = R^2 = R^3$ = H, $R^4R^5 = CH_2O_2$) despite the fact that a sample kindly provided by Professor L. Marion did not show a characteristic rotatory change with solvent polarity. These facts confirm our suggestion that the absolute stereochemistry of the aporphine alkaloids may now be assigned on the basis of the sign of rotation in ethanol or chloroform. The only doubtful case is anolobine (2-hydroxy-5 : 6-methylenedioxyaporphine) whose rotation ($[\alpha]_D$ −23°) is too low for unambiguous assignment.

Now that the absolute stereochemistry of the benzyl*iso*quinoline, morphine, aporphine, and tetrahydroberberine alkaloids is known an interesting pattern emerges. Sinomenine (XLI) is enantiomorphous at $C_{(9)}$ to (−)-sinactine (XXXVIII) and (−)-tuduranine (XLII), which are also found in *Sinomenium acutum* (Goto and Kitasato, *J.*, **1930**, **1234**; Goto, Inaba, and Nozaki, *Annalen*, **1937**, **530**, **142**). Similarly in *Papaver somniferum* thebaine (I), morphine (XII; R = H), and codeine (XII; R = Me) are accompanied by (+)-codamine (XXXII; R^1 = OH, R^2 = OMe) and (+)-laudanosine (XXXII; $R^1 = R^2$ = OMe), and in *Papaver orientale* thebaine (I) and (+)-*iso*thebaine appear at different periods

of growth. In each case the morphine alkaloids are enantiomorphous at $C_{(9)}$ to those mentioned of the other series accompanying them. In addition Hesse (*Annalen*, 1870, **153**, 47; *Ber.*, 1871, **4**, 693; *Annalen*, 1894, **282**, 209) isolated laudanine [(±)-laudanidine] and (−)-laudanidine (XXXIII) from opium residues. As (−)-laudanidine is the only alkaloid of the same absolute stereochemistry as thebaine isolated from opium it is reasonable to accept it, or a less methylated base, as a precursor of thebaine in Robinson and Sugasawa's biogenetic scheme (*J.*, 1931, 3163). The oxide ring may then be built by an allylic expulsion of methoxyl (XL) ⟶ (XLI) ⟶ (I). It is significant that of the benzyl*iso*quinoline alkaloids present in opium only laudanidine has a free hydroxyl group suitable for oxide ring



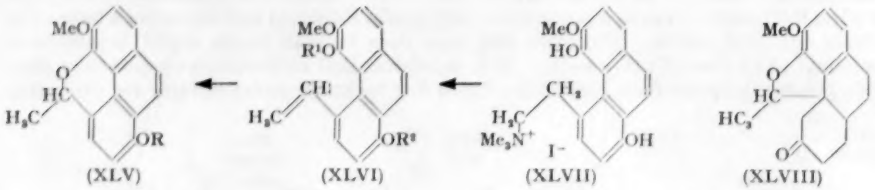
(XLI) (XLII) (XLIII) = (XXXIII) (XLIV)

formation. In *Papaver orientale*, as the plant ripens, the yield of thebaine increases, but when the plant begins to wither the yield of this alkaloid decreases and that of *iso*thebaine increases. This is consistent with the removal of (−)-laudanidine in the formation of thebaine and the accumulation of (+)-laudanidine which is subsequently used to make (+)-*iso*thebaine. On this basis, (+)-*iso*thebaine should be 2(or 4)-hydroxy-3 : 6(or 5)-dimethoxyaporphine. 2 : 3 : 6-Trimethoxyaporphine has been synthesised (Bentley and Blues, unpublished results) and is not identical with *iso*thebaine methyl ether; 3 : 4 : 6-trimethoxyaporphine has already been shown to be identical with morphothebaine dimethyl ether (Gulland and Haworth, *J.*, 1928, 2083). The work of Schlittler and Müller (*Helv. Chim. Acta*, 1948, **31**, 1119) indicates that *iso*thebaine is a 3 : 4 : 5-substituted aporphine, but this has been challenged by Kiselev and Konovalova (*J. Gen. Chem. U.S.S.R.*, 1949, **19**, 148). Further work on this problem is proceeding.

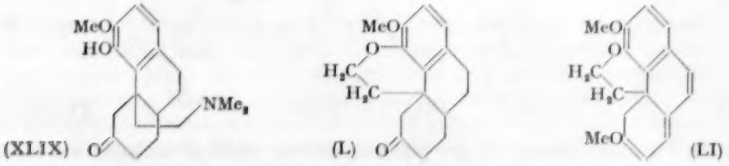
In view of its relevance to Rapoport and Lavigne's degradative work (*loc. cit.*) on the thebenones we have investigated the size of the oxide ring (formed by cyclisation of the 4-hydroxyl group with the ethanamine chain) in thebenol and thebenone derivatives by Kuhn–Roth *C*-methyl determinations. Gulland and Virden (*J.*, 1928, 921) assigned a six-membered oxide ring structure (XLV; R = H) to thebenol, the product of Hofmann degradation of *N*-methylthebenine methiodide (XLVII) (Freund, *Ber.*, 1894, **27**, 2961; Freund, Michaels, and Gobel, *ibid.*, 1897, **30**, 1356; Pschorr and Loewen, *Annalen*, 1910, **373**, 56). This structure, and a mechanism involving the intermediate vinyl compound (XLVI; $R^1 = R^2 = H$) were made very likely by the observation that the vinyl compound (XLVI; $R^1 = R^2 = Me$) cyclised to methebenol (XLV; R = Me) in warm acetic acid (Pschorr and Massaciu, *Ber.*, 1904, **37**, 2780). The structure has now been confirmed by the production of one molecular equivalent of acetic acid on Kuhn–Roth oxidation.

Cahn (*J.*, 1926, 2562) and subsequently Small, Sargent, and Bralley (*J. Org. Chem.*, 1947, **12**, 847) and Bentley, Robinson, and Wain (*J.*, 1952, 958) assigned a similar structure (XLVIII) to thebenone, the product of Hofmann degradation of dihydrothebainone dihydromethine (XLIX). In this case there is evidence (Bentley, Robinson, and Wain (*loc. cit.*) that a vinyl compound is not an intermediate, and the preparation of (LIII) from (LII) was cited as a model for an elimination with rearrangement leading to (XLVIII). This model is, however, unsuitable as bimolecular replacement of $-NH_3^+$ by $-O^-$ is impeded by the *neo*pentyl system, and owing to the absence of a β-hydrogen atom normal elimination is impossible; hence the abnormal reaction observed is the only easy reaction. In the methohydroxide of (XLIX), bimolecular replacement is not impeded and the product (L) is quite normal. This has been confirmed (cf. Rapoport and Lavigne, *loc. cit.*) by the failure to isolate acetic acid after the Kuhn–Roth oxidation of piperonylidene-β-thebenone and of 6-methoxythebentriene (LI).

The oxide rings in thebenol and thebenone are therefore differently constituted, but both are six-membered. The abnormal addition of the phenoxide ion to an olefin in the preparation of thebenol illustrates how a spatial probability factor can bring about an energetically unfavourable reaction.



(XLV) (XLVI) (XLVII) (XLVIII)



(XLIX) (L) (LI)

(LII) $Ph{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_2{\cdot}NMe_3^+ \longrightarrow Ph{\cdot}CH{=}CMe{\cdot}CH_2Me$ (LIII)

Experimental

C-Methyl Determinations.—(i) Thebenol. Found: *C*-Me, 4·2, 6·5. Calc. for one *C*-Me, 5·6%. (ii) 6-Methoxythebentriene and piperonylidene-β-thebenone, no *C*-Me.

Diacetylmorphothebaine.—Morphothebaine (2 g.) was acetylated with acetic anhydride and pyridine at room temperature. The *diacetyl derivative* was purified by chromatography on alumina, 1 : 1 benzene–light petroleum (b. p. 40—60°) being used for elution. The base crystallised from light petroleum (b. p. 60—80°) in pale yellow rods, m. p. 125—128° (Found: C, 69·6; H, 5·9; N, 4·0. $C_{22}H_{23}O_5N$ requires C, 69·4; H, 6·0; N, 3·7%).

Metathebainone Methine Hydrobromide.—The *hydrobromide* was precipitated when metathebainone methine was dissolved in alcoholic hydrobromic acid and recrystallised from 96% ethanol as yellow prisms, m. p. 236—237° (decomp.) (Found: C, 57·1, 57·0; H, 6·1, 6·1; N, 3·3; loss at 120°/vac., 0. $C_{19}H_{23}O_3N,HBr,\frac{1}{4}H_2O$ requires C, 57·6; H, 6·2%). Schöpf and Borkowsky (*loc. cit.*) found for their material prepared from 14-hydroxydihydrothebainone methine, m. p. 230—231° and, after drying at 100°/*in vacuo*, C, 57·1; H, 6·2%.

O-Phenylglyoxylyldihydrocodeine.—Dihydrocodeine (5 g.) and phenylglyoxylyl chloride (3 g.) were kept in pyridine (15 ml.) at room temperature overnight. The mixture was diluted with aqueous sodium carbonate and extracted four times with benzene, and the benzene extracts were repeatedly washed with water, dried (Na_2SO_4), and evaporated. Recrystallisation twice from 1 : 1 benzene–light petroleum (b. p. 100—120°) gave *phenylglyoxylyldihydrocodeine* as colourless prisms, m. p. 171° (Found: C, 72·1; H, 6·3. $C_{26}H_{27}O_5N$ requires C, 72·0; H, 6·2%).

Reaction of Phenylglyoxylyldihydrocodeine with Methylmagnesium Iodide.—A solution of the ester (5 g.) in dry benzene (100 ml.) and dry ether (30 ml.) was slowly added to one of methylmagnesium iodide (4 mols.; from 1·15 g. of magnesium) in ether–benzene. The mixture was left for 3 hr. at room temperature, then boiled under reflux for 3 hr. and decomposed with ammonium chloride solution, the benzene–ether layer separated, and the aqueous layer extracted with chloroform. The organic layers were separately dried and evaporated. The residual oil was boiled under reflux with 5% methanolic potassium hydroxide for 5 hr., and the solution evaporated to small bulk, diluted with water, filtered, extracted with ether, acidified with hydrochloric acid, and extracted five times with ether. The latter extracts were then dried and evaporated leaving a black oil. This was repeatedly extracted with small quantities of boiling light petroleum (b. p. 100—120°); a violet solution was obtained. The combined petroleum extracts, on cooling, deposited 283 mg. of atrolactic acid as colourless needles, $[\alpha]_D^{18}$ −5·73° (*c* 1·4 in EtOH).

The University, Aberdeen.
The Dyson Perrins Laboratory, Oxford.

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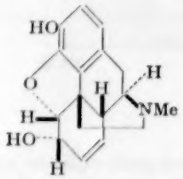
A Crystallographic Examination of the Structure of Morphine.

By Maureen Mackay and Dorothy Crowfoot Hodgkin.

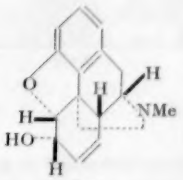
[Reprint Order No. 6276.]

Crystals of morphine hydriodide dihydrate have been examined by quantitative *X*-ray analysis. They are orthorhombic, space group $P2_12_12_1$ with four molecules, $C_{17}H_{19}O_3N,HI,2H_2O$ per unit cell. Parameters for all the atoms in the crystal unit have been derived from calculation of the electron-density distribution projected down the *b* and *c* axes. The molecule is found to be approximately T shaped; the atoms of rings I and II and the oxide ring lie near one plane, while atoms of ring III and the ethanamine ring lie close to a second plane at right angles to the first; this is a consequence of the *cis*-fusion of rings II and III. Details of the stereochemical form of the different rings present are established.

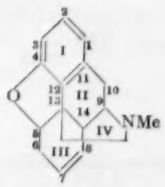
The exact stereochemical structure of morphine presents a chemical problem of considerable complexity. As the preceding paper by Bentley and Cardwell illustrates, the arguments used so far to derive the relations between the five different asymmetric centres in the molecule are often far from conclusive. At Dr. Cardwell's suggestion, we have therefore examined the morphine structure by *X*-ray analysis. We accepted at the outset of our examination the accumulated chemical evidence in favour of the Gulland–Robinson formula for morphine, and a major part of the stereochemical evidence reviewed by Bentley and Cardwell. The problem presented to us accordingly took the form of deciding whether formula (I) or (II) correctly represented the structure of morphine, and of these (I) (or its mirror image) had been supported by Rapoport and Lavigne (*J. Amer. Chem. Soc.*, 1953, **75**, 5329). Our conclusions are, however, independent of our initial structural postulates.



(I)



(II)



Crystals of the hydriodide, hydrobromide, and hydrochloride hydrates of morphine were kindly supplied to us by Dr. Cardwell. As no crystals of the hydrochloride of adequate size were obtained, no measurements were carried out on them. Several oscillation photographs were taken of the hydrobromide, but it was decided to carry out the main *X*-ray analysis on the hydriodide alone; data from this salt could give directly unambiguous results, owing to the high contribution of iodine to the structure factors. Preliminary crystallographic data on both morphine hydriodide and hydrobromide are summarised below.

Crystal Data.—$C_{17}H_{19}O_3N,HI,2H_2O$; *M*, calc. 449; *d*, calc. 1·65, found 1·66. Slightly discoloured yellow orthorhombic needles. Unit-cell dimensions, $a = 20{\cdot}32$, $b = 13{\cdot}02$, $c = 6{\cdot}84$ Å. Space group, $P2_12_12_1$. Four molecules per unit cell. (000) = 616.

$C_{17}H_{19}O_3N,HBr,2H_2O$; *M*, calc. 402; *d*, calc. 1·47, found 1·46. Colourless orthorhombic needles. Unit-cell dimensions, $a = 20{\cdot}07$, $b = 12{\cdot}75$, $c = 6{\cdot}94$ Å. Space group $P2_12_12_1$. Four molecules per unit cell. F(000) = 544.

Structure Analysis.—It was decided that sufficient accuracy would be obtained by working with two-dimensional data only, and intensities were therefore measured for the (*h*0*l*) and (*hk*0) reflections. From the *b*- and the *c*-axis projections of the Patterson function calculated from the derived F^2 values, the *x*, *y*, and *z* co-ordinates of the iodine atoms were found directly; these are: *x*, 0·069; *y*, 0·058; *z*, 0·442.

FIG. 1. *Electron density of morphine hydriodide dihydrate projected on* (001). *Contour lines are drawn at intervals of* 2e Å^{-2}, *except for the iodine ion, where the intervals are arbitrary. The* 1*-electron contour is dotted.*

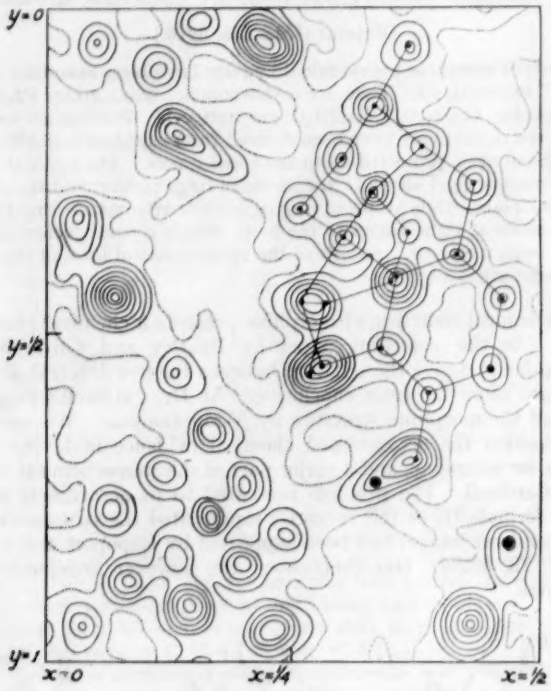
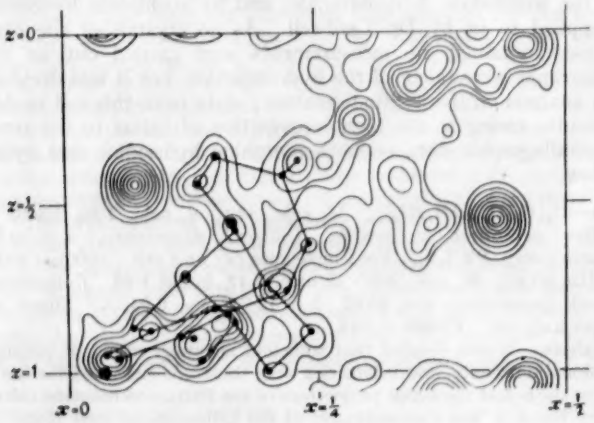
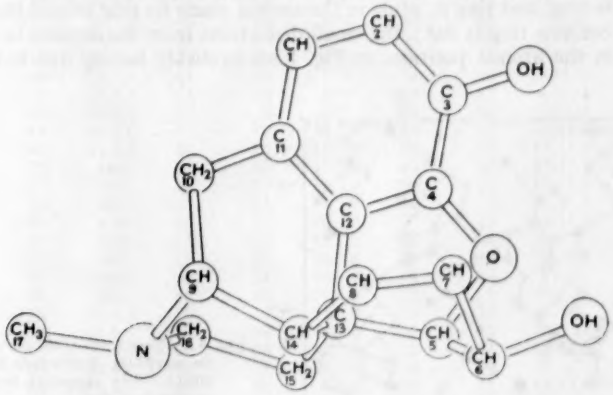


FIG. 2. *Electron density of morphine hydriodide dihydrate projected on* (010). *Contour lines are drawn at intervals of* 2e Å^{-2}, *except for the iodine ion, where the intervals are arbitrary. The first contour is drawn at the* 4*-electron level.*



By using signs based on the contribution of the iodine atoms alone, and the observed structure amplitudes, electron-density projections along the *c* and *b* axes were calculated. Models of the possible structures of morphine were made, and projected on to the electron-density projections, by means of a mirror suitably placed, and a source of parallel light. It was found that the less planar model, *i.e.*, that corresponding to (I) above, exactly fitted the projections. Structure factors were then calculated based on possible positions for all the atoms in the unit cell and, with the corrected signs found, further electron-density projections were derived. In all, three refinements were carried out on each projection, and the latest electron-density distributions calculated are shown in Figs. 1 and 2. By the further use of models projected on these projections, and by calculation of the exact centres of resolved peaks, the atomic

FIG. 3. *Molecule of morphine accurately drawn from final co-ordinates.*



co-ordinates listed in Table 1 were derived. The reliability indices calculated on these co-ordinates were: $R = 13\%$ for ($hk0$) structure factors, and $R = 17\%$ for ($h0l$) structure factors, where

$$R = \frac{\sum\big||F_o| - |F_c|\big|}{\sum|F_o|} \times 100$$

The F_c and the F_o values, for ($hk0$) and ($h0l$) structure factors, are compared in Table 2.

TABLE 1. *Final co-ordinates.*

C at position	*x*	*y*	*z*	C at position	*x*	*y*	*z*
1	0·038	0·553	0·943	14	0·170	0·717	0·582
2	0·050	0·445	0·953	15	0·242	0·690	0·880
3	0·113	0·410	0·892	16	0·200	0·768	1·000
4	0·160	0·480	0·828	17	0·133	0·942	0·967
5	0·242	0·548	0·623	O 3	0·125	0·308	0·900
6	0·217	0·547	0·418	6	0·233	0·440	0·375
7	0·150	0·567	0·358	(oxide)	0·227	0·467	0·758
8	0·133	0·657	0·437	(H_2O)	0·167	0·275	0·533
9	0·118	0·787	0·725	(H_2O)	0·035	0·158	1·000
10	0·065	0·728	0·863	N	0·167	0·848	0·858
11	0·083	0·620	0·875	I	0·069	0·058	0·442
12	0·145	0·580	0·825				
13	0·200	0·647	0·748				

Discussion.—The chemical structure of morphine is confirmed, and the detailed stereochemical form of the molecule in the crystal is established by the two calculated projections of the electron-density distribution shown in Figs. 1 and 2. The relations between the different stereochemical centres are shown in Fig. 3, which corresponds with formula (I) above; from our *X*-ray measurements we have no evidence on the absolute stereochemistry of the molecule.

We have not attempted from our present two-dimensional data to derive accurate

values for bond lengths and bond angles within the molecule. Bond lengths conformed on calculation to the expected values but our limits of error are quite wide. Between the molecules the contact distances are of the order 3·5—4 Å, except in the regions shown in Fig. 4 by the dotted lines. Here the shorter distances suggest a hydrogen-bond system running between the two water molecules and two hydroxyl groups in one molecule, and the nitrogen atom of an adjacent molecule. Around the iodine ions the nearest contacts are with water molecules: I^-–OH_2, 3·54, 3·94 Å; I^-–I^-, 4·12 Å; I^-–N, 4·38, 5·26 Å; I^-–Me, 4·15, 4·14 Å.

The detailed arrangement of the atoms in the molecule appears to be determined by normal stereochemical considerations. Roughly the molecule is T-shaped, with atoms lying close to two planes nearly at right-angles to one another. One plane includes the benzene ring I, the oxide ring, and ring II, while in the second plane lie ring III and the ethanamine ring IV. The benzene ring is flat; the small distortions from the regular hexagonal form which appear in the atomic positions in Fig. 1 are probably largely due to imperfections

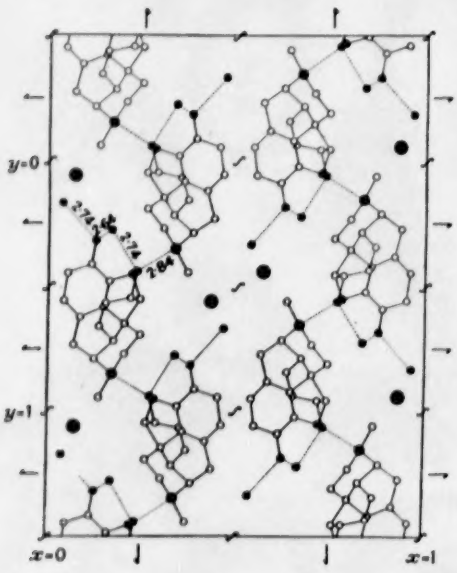


FIG. 4. *Projections of the atomic positions in morphine hydriodide dihydrate on* (001). *The suggested hydrogen-bond system is dotted.*

in our data. On the other hand, the bending of the bonds $C_{(4)}$–O and $C_{(12)}$–$C_{(13)}$ inwards from the regular positions is likely to be real, and required for the formation of the five-membered oxide ring. This ring is, as usual, not planar, $C_{(5)}$ being out of the plane of the other four atoms. The ethanamine ring is of nearly regular chair form; the methyl group is attached to the nitrogen *cis* to the bond $C_{(9)}$–$C_{(10)}$. In ring III the atoms $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, and $C_{(14)}$ lie nearly in one plane, as required by the presence of the 7 : 8-double bond. The nearly boat-shaped form of this ring appears to be required by the packing of the atoms attached to $C_{(6)}$ relative to the atoms of the oxide ring. The arrangement of atoms attached to $C_{(5)}$ and $C_{(6)}$ is not exactly staggered but approximately so, with the hydroxyl group *cis* to the oxygen atom in the oxide ring and in contact with it. Probably the most interesting feature of the structure is the *cis*-junction between rings II and III. The arrangement of these, approximately at right angles to one another, conforms in outline with the configuration found by Bastiansen and Hassel (*Nature*, **1946**, **157**, 765) for *cis*-decalin, though naturally it differs in detail owing to the presence of the double bond in ring III and the benzene ring attached to ring II.

After this investigation had begun, we learnt of similar studies undertaken by Dr. H. Scoloudi and Dr. J. Lindsay, with both of whom we compared conclusions. Dr. Lindsay's

TABLE 2. *Measured and calculated values of the structure factor (hydrogen contributions and unobserved reflections are not included).*

hkl	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)
020	120	148	730	37	− 40	15,6,0	14	10	6,10,0	60	47
040	42	51	830	100	− 83	16,6,0	25	− 26	7,10,0	21	− 19
060	98	− 99	930	34	− 28	17,6,0	31	32	8,10,0	74	58
080	142	−148	10,3,0	101	− 84	19,6,0	34	30	11,10,0	15	21
0,10,0	81	− 93	11,3,0	28	24	22,6,0	12	12	12,10,0	14	− 7
0,12,0	29	− 28	12,3,0	74	− 75	23,6,0	10	− 10	13,10,0	15	13
0,14,0	22	22	13,3,0	30	25	24,6,0	10	10	14,10,0	35	− 35
0,16,0	17	17	14,3,0	20	− 23	170	54	− 45	16,10,0	14	− 14
200	15	− 11	15,3,0	59	68	270	72	60	17,10,0	12	− 10
400	85	− 80	16,3,0	24	23	370	38	− 34	21,10,0	9	− 7
600	120	−125	17,3,0	15	15	470	69	60	1,11,0	27	− 35
800	96	− 97	18,3,0	52	59	570	68	68	2,11,0	27	− 27
10,0,0	84	−113	19,3,0	25	− 20	670	34	41	4,11,0	57	− 65
12,0,0	24	40	20,3,0	41	30	770	91	85	5,11,0	47	42
14,0,0	97	79	21,3,0	14	− 13	870	13	− 13	6,11,0	42	− 36
16,0,0	41	44	22,3,0	13	3	970	31	20	8,11,0	42	16
20,0,0	40	− 41	23,3,0	12	− 10	10,7,0	45	− 45	10,11,0	35	35
22,0,0	39	− 40	24,3,0	20	− 20	11,7,0	24	− 18	12,11,0	24	26
26,0,0	11	12	140	62	55	12,7,0	40	− 45	13,11,0	14	− 11
110	74	70	240	26	− 37	13,7,0	26	− 27	15,11,0	22	− 28
210	30	− 28	340	162	164	14,7,0	15	− 7	18,11,0	16	− 16
310	140	135	440	15	17	15,7,0	77	− 75	19,11,0	14	7
410	110	104	540	57	59	16,7,0	34	25	1,12,0	21	− 21
510	130	−128	740	11	23	18,7,0	14	19	3,12,0	62	− 55
610	24	27	840	26	− 24	19,7,0	14	14	5,12,0	25	− 35
710	104	− 90	940	83	− 87	20,7,0	13	8	6,12,0	25	26
910	120	−115	10,4,1	16	− 16	21,7,0	19	19	8,12,0	15	14
10,1,0	15	− 20	11,4,0	108	− 98	22,7,0	<5	− 2	9,12,0	25	22
11,1,0	70	56	13,4,0	50	− 50	23,7,0	12	14	11,12,0	32	30
12,1,0	17	− 30	14,4,0	14	9	24,7,0	6	− 6	13,12,0	24	27
13,1,0	53	34	15,4,0	24	25	180	12	11	14,12,0	12	− 10
14,1,0	13	− 3	17,4,0	53	48	280	46	− 46	17,12,0	13	16
15,1,0	78	85	18,4,0	15	15	380	21	28	2,13,0	15	− 17
16,1,0	13	5	19,4,0	36	39	480	<8	5	4,13,0	42	− 42
17,1,0	25	24	22,4,0	17	− 9	580	22	22	6,13,0	21	− 21
18,1,0	15	16	24,4,0	<5	− 3	680	85	84	7,13,0	19	− 12
19,1,0	25	− 18	25,4,0	18	− 20	780	22	− 17	8,13,0	20	15
21,1,0	40	− 40	150	21	− 28	880	32	34	10,13,0	32	32
23,1,0	17	− 18	250	115	108	10,8,0	54	54	12,13,0	25	27
26,1,0	10	− 10	350	9	17	11,8,0	25	22	16,13,0	10	− 13
120	53	54	450	91	92	12,8,0	14	− 13	1,14,0	14	− 17
220	62	62	550	23	− 9	14,8,0	52	− 51	3,14,0	23	− 20
320	124	121	650	74	65	15,8,0	15	− 11	4,14,0	13	− 10
420	33	40	750	11	18	16,8,0	35	− 38	5,14,0	24	− 24
520	142	148	850	74	− 60	17,8,0	14	11	8,14,0	12	− 13
620	135	−140	950	46	38	20,8,0	20	20	9,14,0	20	28
720	30	38	10,5,0	123	−111	21,8,0	16	5	11,14,0	21	27
820	78	− 84	12,5,0	67	− 75	190	77	− 85	14,14,0	9	9
920	56	− 58	13,5,0	34	− 27	290	22	− 17	1,15,0	16	16
10,2,0	43	− 62	15,5,0	15	− 10	390	23	− 23	2,15,0	24	− 20
11,2,0	89	− 73	16,5,0	35	20	490	23	− 17	4,15,0	11	− 14
12,2,0	30	23	17,5,0	15	− 18	590	62	60	5,15,0	14	− 15
13,2,0	31	− 42	18,5,0	51	53	690	14	− 7	6,15,0	11	− 8
14,2,0	76	81	20,5,0	24	26	790	54	54	7,15,0	11	− 13
15,2,0	33	32	21,5,0	16	16	890	14	15	10,15,0	9	13
16,2,0	14	17	24,5,0	15	− 16	990	83	82	2,16,0	16	15
17,2,0	59	48	160	10	7	11,9,0	36	− 29	3,16,0	15	− 14
19,2,0	15	− 7	260	38	− 38	13,9,0	53	− 46	6,16,0	23	− 23
20,2,0	20	− 20	360	72	66	14,9,0	15	15	002	170	177
22,2,0	13	− 13	460	15	21	15,9,0	34	− 35	004	13	− 20
23,2,0	12	− 15	560	112	100	17,9,0	14	− 14	006	20	− 29
24,2,0	11	− 17	660	74	66	18,9,0	13	− 6	008	7	7
25,2,0	15	− 13	760	12	24	19,9,0	12	12	101	53	− 56
130	54	62	860	68	59	21,9,0	22	27	201	78	− 90
230	95	95	960	50	− 53	1,10,0	14	− 29	301	50	− 35
330	14	− 14	10,6,0	23	23	2,10,0	24	43	401	67	− 79
430	174	171	11,6,0	94	− 87	3,10,0	34	− 19	501	64	77
530	114	−110	12,6,0	25	− 24	4,10,0	20	− 19	601	12	− 24
630	127	118	14,6,0	52	− 44	5,10,0	14	− 14	701	13	− 13

TABLE 2 (*Continued.*)

hkl	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)
801	23	− 21	16,0,2	43	42	104	109	− 96	15,0,5	7	12
901	111	102	17,0,2	11	− 25	208	28	24	16,0,5	21	24
10,0,1	48	− 41	19,0,2	26	12	304	30	− 48	18,0,5	33	31
11,0,1	136	−142	20,0,2	36	− 35	404	13	14	20,0,5	10	− 16
12,0,1	40	31	21,0,2	34	32	504	60	68	106	27	27
13,0,1	53	− 42	22,0,2	22	− 27	704	80	94	206	11	− 9
15,0,1	44	− 36	23,0,2	19	27	804	34	− 34	306	16	− 17
16,0,1	15	27	24,0,2	9	− 8	904	15	19	506	16	17
17,0,1	62	− 60	103	15	− 33	10,0,4	25	23	606	20	30
18,0,1	23	20	203	53	52	11,0,4	11	11	706	22	27
19,0,1	70	63	303	75	− 77	12,0,4	39	− 25	806	14	10
21,0,1	8	14	403	59	− 60	13,0,4	21	− 17	906	16	16
22,0,1	6	2	503	11	− 12	14,0,4	8	3	10,0,6	11	− 4
23,0,1	16	− 16	603	59	− 62	15,0,4	51	− 53	11,0,6	7	7
25,0,1	25	34	703	9	5	17,0,4	21	− 26	15,0,6	15	− 15
102	190	−203	803	59	− 70	19,0,4	27	17	16,0,6	11	− 12
202	106	114	903	42	46	20,0,4	9	3	107	15	14
302	30	34	10,0,3	57	− 41	21,0,4	28	30	207	13	7
402	32	− 21	11,0,3	59	− 69	22,0,4	13	− 1	307	17	19
502	76	86	12,0,3	55	71	105	10	19	507	10	− 6
602	74	− 63	13,0,3	11	− 11	205	44	44	807	15	− 16
702	64	92	14,0,3	20	17	405	50	− 61	907	14	− 14
802	74	−102	15,0,3	22	− 15	505	15	− 20	10,0,7	9	− 4
902	42	33	16,0,3	59	47	705	21	− 17	11,0,7	6	7
10,0,2	44	− 50	17,0,3	40	− 22	805	11	− 13	108	12	− 8
11,0,2	28	37	18,0,3	43	43	10,0,5	48	− 53	208	11	14
12,0,2	34	8	19,0,3	26	34	11,0,5	14	13	408	8	8
13,0,2	72	− 60	20,0,3	32	− 28	12,0,5	40	39	608	7	− 3
14,0,2	50	48	23,0,3	14	11	13,0,5	14	12			
15,0,2	60	− 49	24,0,3	34	− 24	14,0,5	11	11			

work on codeine hydrobromide gives detailed results in agreement with ours and is being published in *Acta Crystallographica*. Dr. Scoloudi's work on morphine hydriodide has not been completed. She did, however, reach similar conclusions to ours on the stereochemistry of morphine from her first calculated electron-density projections.

EXPERIMENTAL

Preparation and Chemical Analysis of Crystals.—The hydriodide was crystallised from water on evaporation, forming slightly discoloured yellow needles (Found : C, 45·3; H, 5·4; N, 3·4; loss at 100° *in vacuo*, 7·4. Calc. for $C_{17}H_{19}O_3N,HI,2H_2O$: C, 45·4; H, 5·3; N, 3·1; loss, 8·0%).

The hydrobromide crystallised in clusters of fine, colourless needles, by slow evaporation from water, under reduced pressure (Found : C, 50·8; H, 5·8; loss at 100° *in vacuo*, 7·4. Calc. for $C_{17}H_{19}O_3N,HBr,2H_2O$: C, 50·7; H, 6·0; loss 9·0%).

X-Ray Measurements.—Copper-$K\alpha$ radiation was used throughout. The intensities of the (*hk*0) and (*h*0*l*) reflections were estimated visually from Weissenberg photographs, using the multiple-film technique. These intensities were subsequently put on to an approximately absolute scale by Wilson's method (*Nature*, **1942**, **150**, 151), which gave values lower than the final values taken. The latter were obtained by plotting the calculated structure factors divided by the unscaled observed structure factors against $\sin^2\theta$; this method was used also for determining the temperature factor for the final structure-factor calculations. Of a possible 348 (*hk*0) reflections, 272 were measured, and of a possible 180 F(*h*0*l*) reflections 145 were measured. The unit-cell dimensions were determined accurately by calibration against the diffraction pattern of a fine copper wire, recorded on the edges of Weissenberg films.

Calculations.—All Fourier series summations were performed on a Hollerith Tabulator, and at intervals of 1/60 along all three axes. When F^2 values were used for the summation, these values were sharpened by multiplication by the reciprocal of the scattering factor for nitrogen. The structure-factor calculations were carried out by a modification of the process used for Fourier series summation (see, *e.g.*, Booth, " Fourier technique in *X*-ray organic structure analysis," Cambridge University Press, 1948, p. 59), x co-ordinates were approximated first to the nearest 1/1000, and values for $\left\{\begin{matrix}\cos\\ \sin\end{matrix}\right\} 2\pi hx$ were written out from Buerger's tables.

y and z co-ordinates were approximated to the nearest 1/120 of b and c, and the summations of $\begin{Bmatrix}\cos\\\sin\end{Bmatrix} 2\pi hx$, $\begin{Bmatrix}\cos\\\sin\end{Bmatrix} 2\pi \begin{Bmatrix}hy\\lz\end{Bmatrix}$ necessary carried out on the Hollerith Tabulator over all the atoms except iodine, the individual atomic contributions in this sum being weighted oxygen 9, nitrogen 7, and carbon 6. The sums for each *hkl* reflection were multiplied by figures obtained from a normalised McWeeney scattering curve for nitrogen and added to the separately completed contributions for the iodide ion, for which the James and Brindley f curve for iodine was employed. For the (*hk*0) structure factors a temperature factor $B = 3{\cdot}4 \times 10^{-16}$ was applied to all atoms. For the (*h*0*l*) structure factors a temperature factor $B = 3{\cdot}1 \times 10^{-16}$ was applied to all atoms other than iodine, to which an anisotropic one was applied (see, *e.g.*, Cochran, *Acta Cryst.*, 1954, **7**, 503), *viz.*, $B = 2{\cdot}2 \times 10^{-16}$ along the a axis, and $B = 4{\cdot}0 \times 10^{-16}$ along the c axis.

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The Solvolysis of 1-*Chloro-2-methylpropan-2-ol.*

By G. J. Harvey, N. V. Riggs, and V. R. Stimson.

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The kinetics of solvolysis of 1-chloro-2-methylpropan-2-ol in water and aqueous ethanol have been examined. The results are consistent with the assumption that *iso*butyraldehyde is produced from previously formed 2-methylpropane-1 : 2-diol.

In a kinetic investigation of the hydrolysis of ethylene halogenohydrins, Cowan, McCabe, and Warner (*J. Amer. Chem. Soc.*, 1950, **72**, 1194) found that only traces of acetaldehyde were produced, the main product being glycol. Various workers (*e.g.*, Groll and Kautter, U.S.P. 2,042,225; *Chem. Abs.*, 1936, **30**, 4872) have found *iso*butyraldehyde to be produced in good yield when 1-chloro-2-methylpropan-2-ol is refluxed with water. The latter aldehyde could have arisen by pinacolinic rearrangement of 2-methylpropane-1 : 2-diol previously formed in the reaction (cf. Hearne, Tamelle, and Converse, *Ind. Eng. Chem.*, 1941, **33**, 805). The kinetics of solvolysis of 1-chloro-2-methylpropan-2-ol are now reported.

Experimental

Materials.—(*a*) 1-Chloro-2-methylpropan-2-ol (*iso*butylene α-chlorohydrin), prepared by the method of Burgin, Hearne, and Rust (*Ind. Eng. Chem.*, 1941, **33**, 385), had b. p. 121°/680 mm.; they give b. p. 126·7°. After fractionation through a vacuum-jacketed column, 30 cm. long and 1·5 cm. in diameter, packed with $\frac{1}{16}$ in. Dixon rings and fitted with a Whitmore–Lux head, it had b. p. 64·8—65·0°/66 mm., $n_D^{19\cdot6}$ 1·4400. Petrov (*J. Gen. Chem. U.S.S.R.*, 1945, **15**, 690; *Chem. Abs.*, 1946, **40**, 5698) reports b. p. 56·6—57·5°/50 mm., n_D^{20} 1·4392.

(*b*) 2-Methylpropane-1 : 2-diol, prepared from 1 : 2-epoxy-2-methylpropane by the action of dilute sulphuric acid (0·03N), had b. p. 93°/20 mm., n_D^{16} 1·4370 (Found : C, 52·8; H, 11·4. Calc. for $C_4H_{10}O_2$: C, 53·2; H, 11·2%). It gave the bisphenylurethane of m. p. 140° (Krasuskii and Movsum, *Chem. Abs.*, 1937, **31**, 1377). A trace of *iso*butyraldehyde (5%), identified as its 2 : 4-dinitrophenylhydrazone, m. p. 181°, was also obtained.

(*c*) The ethanol used was obtained by distillation of commercial absolute alcohol successively over 5% of concentrated sulphuric acid and sodium hydroxide pellets in the presence of silver oxide. It was dried by being refluxed over, and was distilled from, magnesium ethoxide. Head and tail fractions were rejected at each distillation. Aqueous ethanol mixtures, nominally "v%," were prepared by mixing v volumes of purified ethanol with $100 - v$ volumes of doubly distilled water at room temperature.

Products.—(*a*) 1-Chloro-2-methylpropan-2-ol (1·2 g.) was refluxed in water (25 ml.)for 29 hr. (temperature not measured). A solution of 2 : 4-dinitrophenylhydrazine (500 mg.) in concentrated sulphuric acid (1 ml.) was rapidly diluted with water (50 ml.) and added to the reaction mixture. The bulky yellow precipitate was collected after 24 hr., washed thoroughly with water, dried, and extracted with benzene; the residue on evaporation weighed 350 mg. The crude product had m. p. *ca.* 165° and, once recrystallised from aqueous alcohol, m. p. *ca.* 175°. Chromatography of a benzene solution on alumina gave a sharply defined initial fraction containing the bulk of the product which had m. p. 178—180° on recrystallisation from alcohol. A number of other yellow bands appeared on the column but the various small residues were not further examined. The product was therefore substantially *iso*butyraldehyde, traces of other carbonyl-containing substances being also present.

(*b*) 2-Methylpropane-1 : 2-diol and dilute hydrochloric acid readily gave *iso*butyraldehyde, identified as above.

Kinetic Measurements.—(i) Stock solutions of known concentration from which a (see below) was calculated were prepared from a quantity of the chlorohydrin weighed into a calibrated flask and made up to the mark with the required aqueous ethanol mixture. Pipetted portions (5 ml.) were sealed in Pyrex-glass bulbs which were placed in the thermostat and, after a measured time, the liberated acid was titrated with 0·01N-sodium hydroxide or -barium hydroxide with a methyl-red–bromocresol-green indicator (Bartlett and Swain, *J. Amer. Chem. Soc.*, 1949, **71**, 1407), no interference from atmospheric carbon dioxide being observed.

The thermostats were steady to 0·1°. First-order rate constants were calculated from the expression $k = (1/t) \cdot \log_e[a/(a - x)]$, where a is the initial concentration of chlorohydrin and x is the decrease in its concentration (calculated from the titre) after time t. A typical run is shown in Table 1.

TABLE 1. *1-Cloro-2-methylpropan-2-ol in water at* 97·2°.

c_0, 3·49 × 10^{-3} mole/l.; a, 17·45 × 10^{-5} mole/bulb; NaOH, 0·0116N.

t (min.)	134	196	321	386	446	519	577	655	712	825	899	1002
Titre (ml.)	2·52	3·54	5·46	6·34	7·06	7·76	8·28	9·05	9·51	10·37	10·63	11·18
10^5k (sec.$^{-1}$)	2·27	2·28	2·37	2·38	2·37	2·33	2·32	2·35	2·37	2·37	2·32	2·28

Mean k = 2·33 × 10^{-5} sec.$^{-1}$.

TABLE 2. *Solvolysis of 1-chloro-2-methylpropan-2-ol in aqueous ethanol.*

EtOH (%)	Temp.	10^2c_0 (moles/l.)	10^5k (sec.$^{-1}$)	Temp.	10^2c_0 (moles/l.)	10^5k (sec.$^{-1}$)	E (kcal./mole)		$\log_{10} A$ (sec.$^{-1}$)
0	97·2°	3·49	2·33	85·5°	3·74	0·69	27·4	27·0	11·3
0	97·0	1·99	2·25	84·4	1·83	0·63	26·9	26·0	—
20	97·2	3·67	1·78	85·5	3·67	0·55	26·4		10·8
40	97·1	3·62	1·00	85·1	3·68	0·31	25·7		10·2
60	97·2	3·58	0·52	85·1	3·89	0·160	25·6		9·9
80	97·0	3·36	0·213	85·1	3·75	0·069	24·8		9·1

TABLE 3. *Yields of* iso*butyraldehyde and hydrochloric acid from 1-chloro-2-methylpropan-2-ol in water at* 97°.

Time (hr.)	7	9	27	62
C_4H_8O (mol.)	0·19	0·32	0·78	0·95
HCl (mol.) [a]	0·45	0·53	0·90	0·99
C_4H_8O/HCl	0·42	0·60	0·87	0·96

[a] Calc. from the rate equation.

TABLE 4. *Yields of* iso*butyraldehyde from 2-methylpropane-1 : 2-diol in* 0·24N-*hydrochloric acid at* 97°.

Time (min.)	16	31	123	1260
C_4H_8O (mol.)	0·16	0·23	0·56	0·99

k_1 of the order of 1·5 × 10^{-4} sec.$^{-1}$.

The data and results for the experiments made, together with the values of E and A derived from the Arrhenius equation, $k = Ae^{-E/RT}$, are collected in Table 2.

(ii) Portions (5 ml.) of a solution of the chlorohydrin (0·884 g.) in water (25 ml.) were sealed

in glass bulbs and heated in a bath at 97° for the given times, the weights of crude *iso*butyraldehyde 2 : 4-dinitrophenylhydrazone then being determined as above. The results are shown in Table 3.

(iii) Portions (5 ml.) of a solution of 2-methylpropane-1 : 2-diol (0·802 g.) in 0·24N-hydrochloric acid (25 ml.) were treated as above. The yields of chromatographed *iso*butyraldehyde 2 : 4-dinitrophenylhydrazone are used in Table 4, to show that the rate of this reaction in 0·02N-acid would be about half that of the solvolysis of the chlorohydrin, proportionality of rate to acid concentration being assumed.

Discussion

Course of the Solvolysis in Water.—The rate of production of acid during solvolysis of 1-chloro-2-methylpropan-2-ol follows simple first-order kinetics to at least 75% reaction, the rate constants being independent of initial concentration. *iso*Butyraldehyde is produced ultimately in 100% yield, but Table 3 shows that a reaction yielding this product takes place subsequently to the production of acid. Production of some *iso*butyraldehyde in a reaction simultaneous with that producing acid is not excluded, but the assumption of production of glycol as an intermediate in the solvolysis and its rearrangement as the subsequent reaction is feasible since, in the presence of 0·02N-hydrochloric acid, 2-methylpropane-1 : 2-diol would be converted into *iso*butyraldehyde at about half the rate of the solvolysis. Protonated oxide may be a precursor of the glycol which is rapidly produced in substantial yield with only a trace of *iso*butyraldehyde by the action of dilute acid on the oxide.

Effects of Solvent Composition.—The first-order rate, which is 5·5 times that of ethylene chlorohydrin in water (Table 5), decreases with increasing ethanol content of the medium, the reaction in water being about ten times as fast as that in "80%" ethanol. The ratio of rates in "60%" and "80%" ethanol is 2·4, which is comparable with the values quoted for typical bimolecular solvolyses and very much smaller than those for typical unimolecular solvolyses (Dostrovsky and Hughes, *J.*, 1946, 166). Winstein and Grunwald (*J. Amer. Chem. Soc.*, 1948, **70**, 828) suggested that marked neighbouring-group participation would occur in solvolysis of a compound of the present type and that, in such a unimolecular solvolysis, "an internal variety of a bimolecular displacement," the rate would show

Table 5. *Aqueous solvolysis of halogenohydrins.*

	10^5k at 97° (sec.$^{-1}$)	E (kcal./mole)	$\log_{10} A$ (sec.$^{-1}$)
1-Chloro-2-methylpropan-2-ol	2·25	27·0	11·3
Ethylene chlorohydrin	0·40 [a]	26·4 [b]	10·2 [b]
Ethylene bromohydrin [c]	6·1	26·8	11·7

[a] Determined for comparison by Mr. I. K. Gregor. [b] Calc. from the rate measurements of Radulescu and Muresanu (*Bul. Soc. stiinte Cluj*, 1932, **7**, 129; *Chem. Abs.*, 1933, **27**, 2085). [c] Calc. from the rate measurements of Cowan, McCabe, and Warner (*loc. cit.*).

less dependence on solvent composition than in unimolecular solvolyses not involving participation (S_N1). The present value differs only slightly from that for ethylene bromohydrin (2·2; calculated from the results of Cowan, McCabe, and Warner, *loc. cit.*) where participation is estimated to be small (Winstein and Grunwald, *loc. cit.*).

The values of E and A for the solvolysis appear to decrease steadily with increasing ethanol content of the medium but the magnitude of the effect cannot be assessed owing to experimental inaccuracies. The values in water are the most accurate and are comparable with those found for the aqueous solvolysis of other halogenohydrins (cf. Table 5).

We thank Mr. I. K. Gregor for the measurement on ethylene chlorohydrin.

University of New England, Armidale, N.S.W., Australia. [*Received, March 17th*, 1955.]

Infrared Spectra and Crystallinity. Part III. Poly(ethylene Glycol).*

By W. H. T. Davison.

[Reprint Order No. 6319.]

Infrared spectra of poly(ethylene glycol) in the molten and the crystalline state are reported; crystalline samples oriented by rolling were examined with polarised radiation. The spectra indicate an essentially *gauche* configuration of the O·$[CH_2]_2$·O portion of the polymer chain and all the main absorptions are assigned by comparison with *gauche* ethylene dichloride. The observed dichroisms support the assignments and also show that the chain is oriented obliquely to the direction of stretch. This orientation is consistent with the highly crumpled helical structure suggested by *X*-ray measurement.

On melting, there is a loss of sharpness of some bands, but the O·$[CH_2]_2$·O grouping largely retains its *gauche* configuration; the main rotation is probably about the CO bonds.

No previous spectroscopic studies of poly(ethylene glycol) are known, but *X*-ray diffraction measurements (Barnes and Ross, *J. Amer. Chem. Soc.*, 1936, **58**, 1129) have shown that it has the same crystal structure as poly(ethylene oxide) (Sauter, *Z. phys. Chem.*, 1933, *B*, **21**, **161**; Fuller, *Rubber Chem. and Tech.*, 1941, **14**, 323). The repeating unit is $[(CH_2)_2O]_p$ and the dimensions of the unit cell show that the chain has a very crumpled configuration.

In this paper infrared spectra of the polymer in the amorphous and the crystalline state are used to study the configuration of the chain. In the absence of a complete *X*-ray analysis, we attempt to establish the configuration and arrangement of the polymer in the crystal lattice, using oriented samples and polarised radiation.

Experimental

Samples of poly(ethylene glycol) of different origins and molecular weights were examined; they differed mainly in the degree of crystallinity shown at room temperature. A sample of $M = 6000$ showed the maximum crystallinity and this was used for the spectra in Figs. 1 and 2. It was examined several times under each of the following conditions: (*a*) melted and allowed to recrystallise between rock-salt plates; (*b*) dispersed in potassium chloride by the pressed-disc technique (Ford and Wilkinson, *J. Sci. Instr.*, 1954, **31**, 338); (*c*) rolled between sheets of silver chloride during solidification to obtain oriented, crystalline samples. Samples (*a*) and (*b*) were examined crystalline, amorphous (at 80°), and after being recrystallised.

The spectra of the polymer which had been allowed to crystallise between rock-salt plates (shown as a dot-dash line in Fig. 1) showed considerable differences from those measured in potassium chloride (full line in Fig. 1) or between silver chloride plates. The crystalline spectra between rock-salt plates showed only weak shoulders at 1345 and 960 cm.$^{-1}$, in contrast to the strong bands observed at these frequencies in other spectra.

Spectra measured with the rock-salt plates at an angle to the beam showed these absorptions more intensely; it follows that they had been weakened by orientation normal to the plane of the sample. Similar orientation also occurred with samples rolled between silver chloride plates; in favourable cases, however, a high degree of orientation was achieved along the direction of rolling.

No difficulty was experienced when heating the potassium chloride discs to melt the polymer (Fig. 1); recrystallisation was slower than normal but showed the same degree of crystallinity as the original discs (Part II, *loc. cit.*). The potassium chloride pressed discs were made in a die designed by Ford and Wilkinson (*loc. cit.*).

Polarised measurements were made with a five-plate silver chloride transmission polariser placed immediately before the entrance slit, double-beam operation being used. The efficiency of polarisation was such that a pair of identical crossed polarisers transmitted only 5% of the radiation transmitted by the same polarisers when parallel to each other.

All measurements were made with a Grubb-Parsons S.3/DB1 double-beam spectrometer

* Part II, *J.*, 1955, 2431.

with sodium chloride prism. Re-examination of the 2000-cm.$^{-1}$ region with a lithium fluoride prism failed to resolve the CH stretching region.

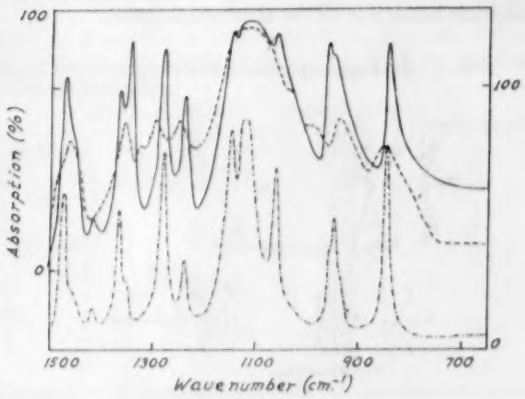


FIG. 1.

Poly(ethylene glycol) :
———— *Crystalline in* KCl *disc.*
– – – – – *Molten in* KCl *disc.*
—·—·— *Crystalline between* NaCl *plates (displaced downward).*

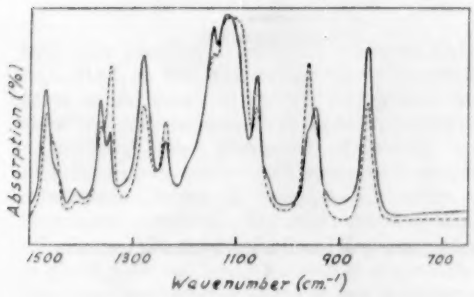


FIG. 2.

Oriented, crystalline poly(ethylene glycol) :
———— *With perpendicularly polarised radiation.*
– – – – – *With parallel polarised radiation.*

DISCUSSION

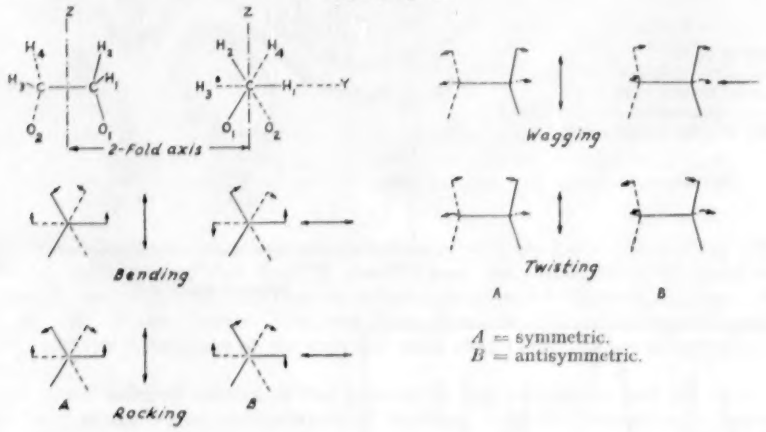
X-Ray studies (Sauter, *loc. cit.*; Fuller, *loc. cit.*) show that crystalline poly(ethylene glycol) has a very crumpled chain in which nine repeating units occur in a fibre period of 19·5 Å. Although this suggests a helical structure, it is insufficient to decide the configuration and we will try to establish this from the infrared spectrum of the crystalline polymer. Since the CH_2 rocking modes in the 700—1000-cm.$^{-1}$ region are particularly sensitive to configuration (Brown and Sheppard, *Trans. Faraday Soc.*, 1952, **48**, 128; Brown, Sheppard, and Simpson, *Phil. Trans.*, 1954, *A*, **247**, 35) we use these to decide the configuration of the O·$[CH_2]_2$·O portion of the chain.

Although it is not strictly permissible to apply the selection rules for an X·$[CH_2]_2$·X molecule to a polymer, vibrations which are formally forbidden in the smaller molecule should still be relatively weak in the less symmetrical polymer. If the configuration of this group were *trans* (symmetry C_{2h}) there should be one strong rocking absorption (A_u) at about 773 cm.$^{-1}$ and a weak absorption at about 992 cm.$^{-1}$ (B_g, formally forbidden). A *gauche* configuration (C_2) should show two strong bands at about 880 cm.$^{-1}$ (B) and 944 cm.$^{-1}$ (A). The frequencies quoted are those of ethylene dichloride (Brown and Sheppard, *loc. cit.*); this molecule is the closest model which has been analysed in sufficient detail. Some frequency shifts would be expected between the dihalide and the poly(ethylene glycol), but these cannot be predicted; mass effects alone should raise the frequencies somewhat (cf. ethylene dibromide frequencies).

The two strong absorptions observed in the crystalline polymer at 844 and 947, 960 cm.$^{-1}$ (the origin of the doublet will be discussed later) are in better agreement with a

gauche- than with a *trans*-configuration. We therefore provisionally assign the remainder of the bands of the polymer on the basis of the frequencies of *gauche* ethylene dichloride (see Table) and check the consistency of these assignments by the relative intensities and dichroic behaviour of the absorption bands.

FIG. 3. *Hydrogen deformation modes of gauche* O·$[CH_2]_2$·O *group*; ⟷ *indicates direction of change of dipoles.*



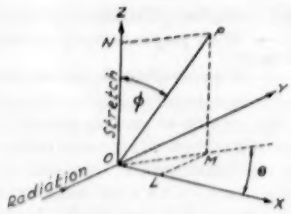


FIG. 4. *Orientation of absorber in singly-oriented specimen.*

The relative intensities of the bands are in good agreement with those of ethylene dichloride except that the twisting modes are stronger. From the movement of the hydrogen atoms only (Fig. 3) we would expect the twisting modes to be inactive; in the dihalide the *A* mode is only observed as a Raman shift and the *B* mode as a weak infrared absorption. However, this is an over-simplified picture and the twisting modes also involve skeletal movement and interaction with skeletal vibrations. Any skeletal interactions or relaxation of symmetry in the polymer would therefore increase the intensities of these bands.

All vibrations of species *A* must have dipole changes parallel to the two-fold axis, from symmetry considerations (see Table 55, Herzberg, "Infra-red and Raman Spectra of Polyatomic Molecules," Van Nostrand Co., N.Y., 1945). Vibrations of species *B* must have dipole changes in the plane perpendicular to the axis, but it is not possible to decide the direction by symmetry.

Considering the movements of the hydrogen atoms alone, the probable directions of dipole changes of the *B* vibrations are as shown by double-headed arrows in Fig. 3; the dipole vectors for the *A* and *B* twisting modes will be particularly sensitive to interaction with other modes. The assignments can therefore be tested by checking whether vibrations which have the same dipole vector have the same dichroic behaviour. All *A* deformation modes have parallel dichroism and all *B* modes have perpendicular dichroism; this is consistent with the provisional assignments.

Each of the doublets at **947, 960**, and at **1344, 1362** cm.$^{-1}$ consists of two components of strong, but opposite dichroism; the dichroisms of the components are markedly higher than of the single bands. The splitting of these *A* fundamentals is attributed to coupling between vibrations in the crystalline state. A similar explanation has been advanced for the 720-cm.$^{-1}$ doublet of crystalline polyethylene (Stein and Sutherland, *J. Chem. Phys.*, 1954, **22**, 1993; Krimm, *ibid.*, p. 567). From the model of the helix which we propose

Assignment	C_2	Dipole change (Fig. 3)	Ethylene dichloride	Poly(ethylene glycol)	Dichroism
$(CH_2)_2$ Bending	*A*	*Z*	1433 (s)	1455 (sh)	∥
	B	*Y*	1429 (R)	1470 (s)	⊥
$(CH_2)_2$ Rocking	*A*	*Z*	944 (s)	947 (sh)	⊥ } ∥
				960 (s)	∥ }
	B	*Y*	880 (s)	844 (s)	⊥
$(CH_2)_2$ Wagging	*A*	*Z*	1312 (s)	1362 (w)	⊥ } ∥
				1344 (s)	∥ }
	B	*X*	1286 (s)	1280 (s)	⊥
$(CH_2)_2$ Twisting	*A*	(*Z*)	1207 (R)	1237 (m)	∥
	B	?	1143 (w)	1145 (s)	⊥
C–C Stretching	*A*	(*Z*)	1032 (m)	*ca.* 1100 (sh)	∥
C–O–C Stretching	Antisym.	—	—	1120 (vs)	⊥
	Sym.	—	—	*ca.* 1061 (m)	⊥

[Intensities are shown as very strong (vs), strong (s), medium (m), or weak (w); shoulders are shown as (sh). R indicates that the vibration is only observed in the Raman effect.]

later, the coupling is probably between repeating units in the helix (Higgs, *Proc. Roy. Soc.*, 1953, *A*, **220**, 472) rather than between helices in the crystal lattice. Either explanation would result in strictly orthogonal vibrations and explain why these components show higher dichroisms than those of the other absorption bands.

Although some interaction of skeletal stretching vibrations will occur, the crumpled or helical configuration will make such coupling less extensive than in planar long-chain compounds (Brown, Sheppard, and Simpson, *loc. cit.*) and we consider it possible to neglect long-range coupling. The main coupling will probably occur between the CO stretching vibrations. In dimethyl ether (Herzberg, *op. cit.*, p. 353) there is an anti-symmetric mode at about 1120 cm.$^{-1}$ and a stronger symmetric mode at about 940 cm.$^{-1}$. The former band has been observed in a large number of ethers at about this frequency (Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 101), but the symmetric mode has not generally been characterised. The extent of coupling will be very dependent upon the COC angle and should be reduced by the greater effective mass of the polymer chain.

The type and dichroism of the 950-cm.$^{-1}$ doublet, together with the general consistency of the deformation assignments, prevent our re-assigning this doublet to a CO stretching mode. We tentatively assign the sharp perpendicular 1061-cm.$^{-1}$ absorption of poly(ethylene glycol) to a symmetric COC stretching mode, and the parallel shoulder at about 1100 cm.$^{-1}$ to a CC stretching mode (cf. 1032 cm.$^{-1}$ for *gauche* ethylene dichloride); the parallel dichroism of the latter is consistent with its assignment to an *A* symmetry species.

Highly oriented samples of the crystalline polymer between silver chloride plates showed no signs of double orientation (by measurement of the spectrum of samples inclined to the beam); this would be expected even if the crystals were doubly-oriented since the chain appears to have an odd-number screw-axis. We will therefore assume, at least as an approximation, single orientation, *i.e.*, the various absorbing groups are oriented with respect to the fibre axis (direction of rolling) but randomly distributed about this axis.

Consider the vector of dipole change associated with a given vibrational mode *OP* in the orthogonal reference system shown in Fig. 4. The direction of radiation is *OY*, normal to the fibre axis. Radiation polarised with the electric vector parallel to the fibre axis *OZ* will be absorbed to the same extent whatever the angle θ; the absorption will be proportional to $(OP \cos \phi)^2$. However, perpendicularly polarised radiation will be absorbed by an amount proportional to $(OP \,.\, \sin \phi \,.\, \cos \theta)^2$. As the vectors are randomly distributed with respect to θ, the ratio of the total components absorbing parallel and perpendicular radiation (the dichroic ratio) is obtained by integrating with respect to θ within the limits 0 and $\pi/2$.

The dichroic ratio is therefore given by:

$$\frac{A_{\parallel}}{A_{\perp}} = \frac{\int_0^{\pi/2} (OP \cdot \cos\phi)^2 \cdot d\theta}{\int_0^{\pi/2} (OP \cdot \sin\phi \cdot \cos\theta)^2 \cdot d\theta} = \frac{2}{\tan^2\phi}$$

The same result is obtained, but by a different method, for a helical molecule (Eqn. 10, Higgs, *loc. cit.*). Qualitatively, this means that the observed dichroic ratio must exceed 2·0 before we can deduce that the vibration has a change of dipole inclined at less than 45° to the direction of orientation, *i.e.*, mainly parallel.

Now the mean dichroic ratio of the symmetrical (*A*) wagging, twisting, and rocking CH_2 modes is about 1·6; this means that the two-fold symmetry axis of the O·$[CH_2]_2$·O group is inclined at about 48° to the fibre axis. From the dichroic ratios of the *B* rocking mode (about 0·4) and of the *B* wagging mode (about 0·5) the *X* and *Y* axes of this group must be inclined at about 65° to the fibre axis. While these figures can only be regarded as approximate, they provide a consistent picture of the O·$[CH_2]_2$·O group lying obliquely with the two-fold axis at about 48° and the CC bond at about 65° to the fibre axis. The two COC vibrations have perpendicular dichroisms, from which it follows that both the CC direction and the bisectrix are at about 70° to the fibre axis. The oblique orientation of the methylene and COC groups is consistent with a helical configuration. The unit cell (Sauter, *loc. cit.*) contains four chains within a unit cell of 12 × 9·5 Å, and nine polymer repeating units within a fibre period of 19·5 Å.

The inclination of the C_2 axis with respect to the direction of stretch, combined with the odd number of repeating units in the fibre period, means that the chains have an "up" or "down" sense. The unit cell will therefore probably contain two chains which are upside down with respect to the other two (Bunn, "Chemical Crystallography," Oxford Univ. Press, 1946, p. 321).

By use of Stuart-type atomic models (*Z. phys. Chem.*, 1934, *B*, **27**, 350) and the configuration and orientations deduced above, the best model of the chain which we can construct is a helix with a three-fold screw axis (Fig. 5). Nine polymer repeating units of this model occupy the fibre period of 19·5 Å found by *X*-ray diffraction measurements.

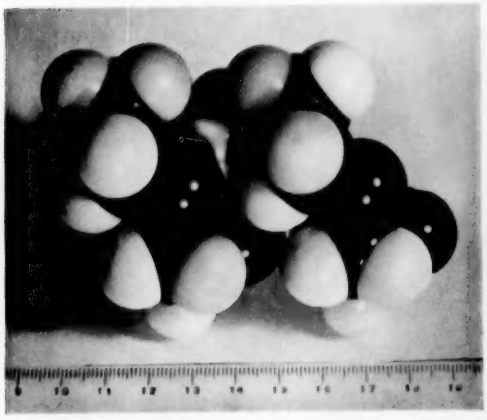
Molten poly(ethylene glycol) has a rather different spectrum from that of the crystalline material (Fig. 1) but the differences are not as marked as for the polyesters (Part I, *J.*, 1955, 2428) or dicarboxylic acids (Part II, *loc. cit.*). There is considerable broadening (and consequent reduction of apparent intensity) of most of the absorptions, but none of the strong bands completely disappears as in the polyesters or dicarboxylic acids. On the other hand, no new strong bands appear as in the *n*-paraffins (Brown, Sheppard, and Simpson, *loc. cit.*) or in ethylene dihalides (Brown and Sheppard, *loc. cit.*).

The configuration of the O·$[CH_2]_2$·O group is therefore substantially the same in the molten state as in the crystalline, *i.e.*, a *gauche* form; in this it is similar to crystalline ethylene chlorohydrin (Mizushima, Shimanouchi, Miyazawa, Abe, and Yasumi, *J. Chem. Phys.*, 1951, **19**, 1477) and a number of other ethylene glycol derivatives (Davison and Corish, unpublished work). Since some rotation must occur on melting it is suggested that this occurs mainly at the CO bonds which have lower barriers to rotation than the CC bonds. The second-order effect of such rotation would account for some of the broadening of the methylene deformation absorptions, which is rather more than would be expected from a change of state alone.

The author thanks Mr. P. J. Corish for obtaining some of the spectra, and Drs. N. Sheppard and J. K. Brown for a helpful discussion of the dipole changes of the methylene deformation modes. He also thanks the Dunlop Rubber Company for permission to publish this work.

Chemical Research Division,
Dunlop Research Centre, Birmingham, 24. [*Received, April 12th*, 1955.]

FIG. 5. *Poly(ethylene glycol).*



[*To face p.* 3274

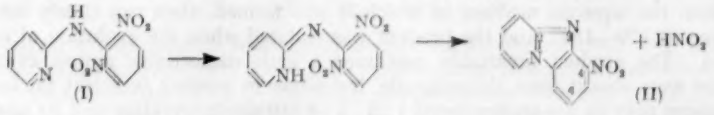
Syntheses in the Pyrido- and Piperido-(1′ : 2′-1 : 2)benziminazole Series.

By K. H. Saunders.

[Reprint Order No. 6351.]

2-Chloro-1 : 3-dinitrobenzene condenses with 2-aminopyridine to form 2-(2 : 6-dinitroanilino)pyridine which at once begins to lose nitrous acid, thus producing 4-nitropyrido(1′ : 2′-1 : 2)benziminazole. 1-*o*-Azidophenylpiperidine is decomposed by heat to yield nitrogen and 2 : 3-dihydropiperido-(1′ : 2′-1 : 2)benziminazole, an unstable reducing agent, which at once gives up hydrogen, preferably to the reaction medium, to yield piperidobenziminazole identical with the reduction product of pyrido(1′ : 2′-1 : 2)-benziminazole. 1-*o*-Azidophenylpiperidine having substituents in the benzene ring, and analogous azides derived from hexahydroazepine, morpholine, and 1-ethoxycarbonylpiperazine undergo the above ring-closure, as does 4-azido-2-nitro-1 : 5-dipiperidinobenzene to form 5-nitro-6-piperidinopiperido-(1′ : 2′-1 : 2)benziminazole, which after reduction again undergoes the same ring-closure reaction to produce a pentacyclic base.

In the preparation of 2-(2 : 6-dinitroanilino)pyridine (I) from 2-chloro-1 : 3-dinitrobenzene and 2-aminopyridine it was observed that after removal of the desired product from the crude reaction mass with boiling benzene there remained an almost equal weight of a yellow substance, m. p. *ca.* 265—270°. The latter proved to be a nitro-compound, reduced by iron–acetic acid to a diazotisable amine which coupled with Brenthol OP (2-hydroxy-3-naphtho-*o*-phenetidide) to a violet dye; and when it was observed that nitrous acid was evolved from the reaction solution it was realised that the substance must be 4-nitropyrido(1′ : 2′-1 : 2)benziminazole (II) produced from the tautomeric form of 2-(2 : 6-dinitroanilino)pyridine by Morgan and Stewart's reaction (*J.*, 1938, 1292):

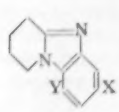


The above reaction was confirmed when it was found that 2-(2 : 6-dinitroanilino)-pyridine yields 4-nitropyrido(1′ : 2′-1 : 2)benziminazole and nitrous acid in boiling glycol monoethyl ether. This unequivocal synthesis shows that Stewart and Morgan's nitropyridobenziminazole is the 6-isomer (see below).

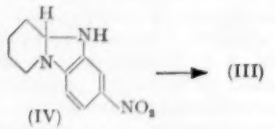
Reduction of 4-nitropyrido(1′ : 2′-1 : 2)benziminazole with hydrogen and platinum oxide in ethanol, as described by Morgan and Stewart (*loc. cit.*) for the 6-nitro-isomer, afforded a mixture of two amines, both diazotisable, one giving a blue and the other a bluish-red colour with Brenthol OP. It seemed likely that in the latter amine the pyridine ring was reduced. This result evoked the question as to whether it would prove possible to prepare the piperidobenziminazole by heating 1-*o*-azidophenylpiperidine, a reaction somewhat analogous to that by which Smith and Brown (*J. Amer. Chem. Soc.*, 1951, **73**, 2435) made carbazole from *o*-azidodiphenyl, thus providing an easier route to this series than *via* the very limited Morgan and Stewart reaction. Indeed, a compound provisionally assigned the constitution (III) was isolated by Spiegel and Kaufmann (*Ber.*, 1908, **41**, 682) among the substances produced from 1-(2 : 4-dinitrophenyl)piperidine by reduction with cold stannous chloride and by them supposed to be formed by interaction of the nitroso-group in 1-(4-nitro-2-nitrosophenyl)piperidine with the spatially close methylene group of the piperidine ring with elimination of water.

If this ionic reaction can take place it was reasonable to suppose that the free-nitrogen radical formed by decomposition of an azido-group in 1-(2-azido-4-nitrophenyl)piperidine would still more readily form a bond to give in the first instance a dihydrobenziminazole derivative. 1-(2-Amino-6-nitrophenyl)piperidine being to hand, it was diazotised, then converted into the azide, which was heated in dichlorobenzene. Nitrogen

was given off beginning at about 130° and rapidly at 160—170° and there resulted a nitro-compound reducible to a diazotisable amine giving a bluish-red colour with Brenthol OP. A diazotisable amine or amines was present mixed with the nitro-compound. This result warranted the preparation of 1-(2 : 4-dinitrophenyl)piperidine, partial reduction and separation of the isomeric aminonitrophenylpiperidine by chromatography and differences in basicity. On diazotisation of the 2-amino-4-nitro-compound, conversion into the azide,



(III): X = NO_2, Y = H
(V): X = H, Y = NO_2
(VI): X = NHAc, Y = H



(IV)

(III)

and heating in dichlorobenzene there was isolated a nitro-compound, m. p. 219—220°, not altered on admixture with a sample of Spiegel and Kaufmann's base (III). Diazotisable amine was also present in the product. A probable source of the latter appeared to be reduction of some of the nitro-compound by the 2 : 3-dihydro-5-nitropiperidino(1′ : 2′-1 : 2)-benziminazole (IV) supposedly first formed from the free radical. Accordingly nitrobenzene was used as the heating medium and afterwards removed from the solutes by evaporation under a vacuum. Extraction of the distillate with dilute acid and titration with standard nitrite showed the presence of 85% of the theoretical weight of aniline, which was also isolated and converted into tribromoaniline. From the residual nitrobenzene Spiegel and Kaufmann's base (III) crystallised in 85% yield.

By analogy with the above, the product of the original experiment with 1-(2-amino-6-nitrophenyl)piperidine was 7-nitropiperido(1′ : 2′-1 : 2)benziminazole (V). Similarly 1-(2-amino-4-chlorophenyl)piperidine yielded the 5-chloro-compound.

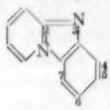
In all subsequent experiments the azide was not isolated but was taken up into nitrobenzene from the aqueous medium in which it was formed, then run slowly into more nitrobenzene at 170—180°, and the product was isolated when the evolution of nitrogen had ceased. The product invariably contained a little diazotisable amine, even when nitro-groups were absent from the molecule, but never in amount sufficient for isolation. The substances may be 1-*o*-aminophenyl-1 : 2 : 3 : 4-tetrahydropyridine and its analogues.

1-(4-Amino-2-nitrophenyl)piperidine was acetylated, and reduced to 1-(4-acetamido-2-aminophenyl)piperidine which produced 5-acetamidopiperidobenziminazole (VI) by the azide synthesis.

The four isomeric monoaminopiperidobenziminazoles have been prepared, their methods of preparation and relation of the two known monoaminopyrido(1′ : 2′-1 : 2)-benziminazoles being set out in the Table in which " M & S " indicate that a substance was first made, or a reaction carried out, by Morgan and Stewart (*loc. cit.*). Morgan and Stewart did not know whether their aminopyridobenziminazole, made from 4 : 6-dinitropyridobenziminazole by partial reduction, deamination, and reduction, was the 4- or 6-isomer. The present unequivocal synthesis of the 4-amino-isomer (II) shows that the Morgan and Stewart route produces the 6-amino-compound. Moreover the reduction of the latter to the 6-aminopiperidobenziminazole also prepared from (VI), proves that the azide synthesis does in fact produce the glyoxaline ring.

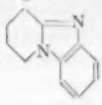
From hexahydroazepine (hexamethyleneimine) were prepared the 1-*o*-aminophenyl, 1-(2-amino-4-chlorophenyl), and 1-(2-amino-4-nitrophenyl) derivatives which were converted *via* the azides into the hexahydroazepino(1′ : 2′-1 : 2)benziminazole (VII) and its 5-chloro- (VIII) and 5-nitro-derivative (IX), the latter being reduced to the amine (X) whence acetylation, nitration, and deacetylation afforded the 5-amino-6-nitro-derivative (XI), deaminated to the 6-nitro-compound (XII) and reduced to the amine (XIII). The amino-group of the amine (X) condensed readily with (*a*) 2-amino-4-chloro-6-methylpyrimidine 1-methiodide, (*b*) twice with adipoyl chloride, and (*c*) formed a urea on treatment with carbonyl chloride. All these derivatives were capable of forming quaternary methiodides.

Pyrido(1′ : 2′-1 : 2)benziminazole, its piperido-analogue, and their monoamino-derivatives.



M. p. 178—179°

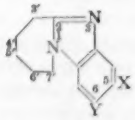
(M & S)



M. p. 101—102° (106°, M & S)

	Deamination of 6-amino- (M & S)	From *o*-azidophenylpiperidine
4-Amino-	M. p. 133—134° Reduction of 4-nitro-deriv. (II)	M. p. 177—177·5°
5-Amino-	Not known	M. p. 218—220° (*a*) Reduction of 5-nitro-deriv. (III) (*b*) Hydrolysis of acetyl deriv. (VI)
6-Amino-	M. p. 230—230·5° (220—230°, M & S) (*a*) Reduction of nitro-compound obtained by deaminating 4-amino-6-nitropyridobenziminazole (M & S) (*b*) Nitration of pyridobenziminazole and reduction	M. p. 198—200°
7-Amino-	Not known	M. p. 186—187° Reduction of 7-nitro-deriv. (V)

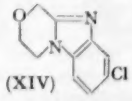
Similarly, 4-(2-amino-4-chlorophenyl)morpholine gave the morpholinobenziminazole (XIV), which owing to the weak directing effect of the chlorine atom yielded several nitro-compounds on nitration in sulphuric acid; from these one pure monoamine of undetermined orientation was isolated.



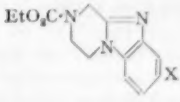
(VII) : X = H, Y = H.
(VIII) : X = Cl, Y = H.
(IX) : X = NO_2, Y = H.
(X) : X = NH_2, Y = H.

(XI) : X = NH_2, Y = NO_2.
(XII) : X = H, Y = NO_2.
(XIII) : X = H, Y = NH_2.

1-Ethoxycarbonylpiperazine was converted into its 4-*o*-aminophenyl and 4-(2-amino-4-chlorophenyl) derivatives from which were obtained the piperazinobenziminazole (XV) and its 5-chloro-derivative (XVI). The yields on ring closure were very poor.



(XIV)



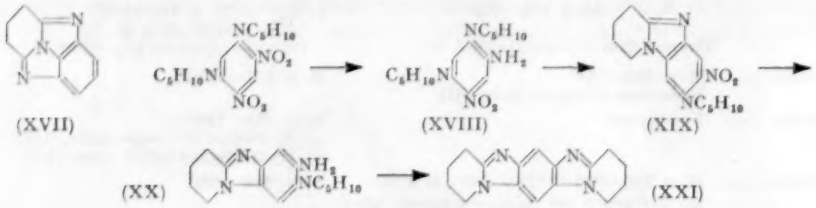
(XV) : X = H.
(XVI) : X = Cl.

Piperido- and the hydroazepino-benziminazole and their substitution products readily form quaternary ammonium compounds. They do not couple in dilute acid solution with diazonium salts, but 4- and 7-aminopiperido(1′ : 2′-1 : 2)benziminazole both couple to form aminoazo-compounds, as do their analogues and 4-aminopyrido-(1′ : 2′-1 : 2)benziminazole. A blue melt is formed with Michler's ketone in phosphorus oxychloride, giving a blue solution on dilution with water, but, unlike Crystal Violet, the coloured substance is destroyed by alkali. Piperidobenziminazole is partly dehydrogenated by palladium–charcoal in an inert gas at 300° in 15—20 minutes, but all is destroyed on longer heating. In experiments to find oxidising agents which would attack the polymethylene chain it was observed that both the piperido- and the hydroazepino-benziminazole, in an inert solvent, combine with one mol. of chlorine, bromine, or iodine. Part of this is given up as free halogen on treatment with aqueous acid and, in the case of chlorine, the benzene ring is then chlorinated.

It is probable that spatial relations are one of the factors which determine whether or not a bridge shall be formed by decomposition of the azido-compound. In general 1-*o*-azidophenylhexahydroazepine and its derivatives afford better yields than do the corresponding pipieridine derivatives, presumably because the distance from the *o*-position of the benzene ring to a methylene group is less in the former case. Steric effects may also account for the observation that, whilst 2-chloro-1 : 3-dinitrobenzene reacts easily with

piperidine, it reacts only slowly with hexahydroazepine, and each base reacts quite differently with 1 : 5-dichloro-2 : 4-dinitrobenzene (see below).

Decomposition of 7-azidopiperido(1′ : 2′-1 : 2)benziminazole gave a tar and no pure substance corresponding to the doubly ring-closed compound (XVII) could be isolated.



(XVII) (XVIII) (XIX) (XX) (XXI)

A double ring-closure to form a fused pentacyclic system was brought about starting from 1 : 5-dinitro-2 : 4-dipiperidinobenzene by the annexed synthesis. The partial reduction [to (XVIII)] was easy but ring closure through the azide to the piperidobenziminazole (XIX) gave only a poor yield, as did further ring closure of the amine (XX) to the pentacyclic base (XXI). Further, 2-aminopyridine does not undergo the Morgan and Stewart reaction with 1 : 5-dichloro-2 : 4-dinitrobenzene in boiling glycol monoethyl ether but condenses twice to form 1 : 5-dinitro-2 : 4-di-(2-pyridylamino)benzene in good yield.

Experimental

Microanalyses by R. Rothwell.

Piperidobenziminazole and its derivatives.

Piperido(1′ : 2′-1 : 2)*benziminazole.*—1-*o*-Aminophenylpiperidine (Lellmann and Just, *Ber.*, 1891, **24**, 2103) (26·4 g., 0·15 mole), dissolved in hydrochloric acid (*d* 1·16; 45 c.c.) and water (200 c.c.), was diazotised at 5—10° with sodium nitrite (10·8 g.) in water (30 c.c.), excess of nitrous acid was destroyed, and the dark orange solution was run during 10 min. with stirring into 20% sodium acetate solution (300 c.c.) containing ice and sodium azide (9·0 g.); the mixture was set aside overnight. The oily azide was collected in nitrobenzene (100 c.c.) and added dropwise down the thermometer arm of a Claisen flask to nitrobenzene (300 c.c.) kept at 165—175°. Nitrogen was smoothly evolved, leaving an orange solution which was evaporated under a vacuum to small bulk (*ca.* 50 c.c.), and the hot liquid poured out to cool. The resulting crystals were collected, washed with cold light petroleum (b. p. 80—100°), and dissolved in hot dilute hydrochloric acid; the solution was boiled with charcoal, filtered, and cooled and the base (12·0 g., 46·5%) precipitated with sodium carbonate. The nitrobenzene filtrate was extracted with dilute hydrochloric acid and worked up as above, yielding more base (7·9 g., 30·5%) containing some diazotisable amine. The first fraction, crystallised three times from ethyl acetate and dried *in vacuo* at 100° for 2 hr., had m. p. 101—102° (Found: C, 76·7; H, 7·2; N, 16·2. Calc. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3%); Morgan and Stewart (*loc. cit.*) give m. p. 106°.

The nitrobenzene removed under vacuum during the concentration was shaken twice with dilute hydrochloric acid; titration with 0·5N-sodium nitrite in presence of potassium bromide showed the presence of 0·042 mole (84%) of aniline. From another portion of the acid solution was obtained 2 : 4 : 6-tribromoaniline, m. p. and mixed m. p. 120°.

Piperido(1′ : 2′-1 : 2)benziminazole formed in ethyl acetate a *monopicrate*, m. p. 229—230° (from glycol monoethyl ether) (Found: C, 51·3; H, 4·4; N, 17·5. $C_{11}H_{12}N_2,C_6H_3O_7N_3$ requires C, 50·9; H, 3·7; N, 17·45%); at 100° with methyl iodide it formed a *methiodide*, m. p. 220—221° (from methanol–acetone) (Found: C, 45·8; H, 6·0; I, 40·3. $C_{12}H_{15}N_2I$ requires C, 45·8; H, 4·8; I, 40·4%); when boiled with iodine in chloroform it gave a brown precipitate of an iodine *addition product*, m. p. 150° (Found: I, 59·5. $C_{11}H_{12}N_2I_2$ requires I, 59·7%).

5-Chloropiperido(1′ : 2′-1 : 2)*benziminazole.*—1-(4-Chloro-2-nitrophenyl)piperidine (Lellmann and Geller, *Ber.*, 1888, **21**, 2283) (24·0 g., 0·1 mole) was reduced overnight in boiling ethanol (200 c.c.) with iron filings (30 g.) and hydrochloric acid (total 14·0 c.c., added during 12 hr.); the mixture, worked up in the usual way, afforded 1-(2-*amino*-4-*chlorophenyl*)*piperidine* (13·7 g., 0·065 mole), b. p. 188—192°/18—20 mm., m. p. 49·5—50° (from methanol) (Found: C, 62·3; H, 7·0; Cl, 17·2. $C_{11}H_{15}N_2Cl$ requires C, 62·8; H, 7·1; Cl, 16·9%). Dilute aqueous

hydrochloric acid produced the *hydrochloride*, m. p. 230—231°, colourless needles from water (Found : Cl^-, 14·2. $C_{11}H_{15}N_2Cl$,HCl requires Cl^-, 14·3%); boiling acetic acid–acetic anhydride yielded the *acetyl* derivative, m. p. 95—96° (from methanol) (Found : C, 61·3; H, 6·0; N, 10·6. $C_{13}H_{17}ON_2Cl$ requires C, 61·8; H, 6·7; N, 11·1%); benzoyl chloride and aqueous sodium hydroxide afforded the *benzoyl* derivative, m. p. 105·0—105·5° (from ethyl methyl ketone) (Found : C, 69·1; H, 6·2; N, 8·6. $C_{18}H_{19}ON_2Cl$ requires C, 68·8; H, 6·0; N, 8·9%). The hydrochloride (37·0 g., 0·15 mole) was dissolved in hydrochloric acid (*d* 1·16; 30 c.c.) and hot water (200 c.c.) and cooled in ice, and the sludge of hydrochloride was diazotised at 5—8° with sodium nitrite (10·5 g.) in water (25 c.c.). After destruction of excess of nitrous acid the deep orange diazo-solution was run into one of sodium azide (12·6 g.) in 20% aqueous sodium acetate (300 c.c.), and the resultant pale yellow oily azide was treated as described above, yielding crude *5-chloropiperido*(1′ : 2·1 : 2)*benziminazole* (25·4 g., 82%), m. p. 151—153°, containing a little diazotisable amine removed by crystallisation from ethylene dichloride; the final m. p. was 153—154° (Found : C, 63·8; H, 5·4; Cl, 17·0. $C_{11}H_{11}N_2Cl$ requires C, 63·9; H, 5·3; Cl, 17·2%). Alternatively the crude base was dissolved in rather more than one equiv. of hot 2N-hydrochloric acid and cooled, affording the *hydrochloride*, m. p. 295—296° (from water) (Found : Cl^-, 14·8. $C_{11}H_{11}N_2Cl$, HCl requires Cl, 14·6%).

5-Nitropiperido(1′ : 2′-1 : 2)*benziminazole* (III).—To 1-(2 : 4-dinitrophenyl)piperidine (Spiegel and Kaufmann, *loc. cit.*) (*ca.* 1 mole) dissolved in boiling ethanol (600 c.c.), was added during 3 hr. a solution of hydrated sodium sulphide (240 g.) and sulphur (32 g.) in water (300 c.c.), and the whole was boiled overnight. The ethanol was removed, the residue extracted with benzene (500 c.c.), and the solution washed with water; the benzene solution was then dried, filtered, and chromatographed on two columns, each 3 × 60 cm. and each containing active alumina (300 g.), giving a lower orange and an upper purple zone; the former was quickly eluted and consisted of 1-(2-amino-4-nitrophenyl)piperidine (*ca.* 47 g.) containing a little unchanged dinitro-compound. Further washing with benzene, until the eluate was straw-coloured, gave a mixture (*ca.* 81 g.) of the above with the isomeric purple 1-(4-amino-2-nitrophenyl)piperidine. The isomers were separated by grinding the solid with N-hydrochloric acid and filtering, the more basic 4-amino-2-nitro-compound dissolving. This process could not be applied to the crude product, a sharp separation not being possible until chromatography had removed gums. The orange isomer was dried, taken up in benzene, and filtered through a 4—5-cm. layer of active alumina, and the benzene removed, leaving crude base (52 g.). The total crude orange base (99 g., 41%) crystallised from benzene–light petroleum (b. p. 80—100°; 1 : 5), yielding pure 1-(2-amino-4-nitrophenyl)piperidine (54 g.), m. p. 96°. Spiegel and Utermann (*Ber.*, 1906, **39**, 2635) give m. p. 86°. The acid filtrate was basified, yielding 1-(4-amino-2-nitrophenyl)piperidine (18 g.) while the dried alumina from the columns extracted with chloroform yielded 11 g. (total 13%). Crystallisation from light petroleum (b. p. 80—100°) yielded the pure base, m. p. 116°. Spiegel and Utermann (*loc. cit.*) give m. p. 116°. In some preparations the orange fraction first obtained from the columns contained a considerable amount of 1-(2 : 4-dinitrophenyl)piperidine. This was separated by dissolving the whole in hydrochloric acid (*d* 1·16), diluting to *ca.* 3 vols., filtering off the precipitated dinitro-compound, and basifying the filtrate to recover 1-(2-amino-4-nitrophenyl)piperidine. For ring closure complete removal of the dinitro-compound was not necessary, as it was easily removed after diazotisation.

1-(2-Amino-4-nitrophenyl)piperidine (39 g.) was dissolved in hydrochloric acid (*d* 1·16; 35 c.c.) and hot water (250 c.c.), the solution was cooled to 5—7°, and the suspension of hydrochloride diazotised with sodium nitrite (12·5 g.) in water (25 c.c.); excess of nitrous acid was destroyed and the deep orange solution filtered from 1-(2 : 4-dinitrophenyl)piperidine (7·0 g.), then run during 10 min. with stirring into 20% aqueous sodium acetate (300 c.c.) containing sodium azide (12 g.). 1-(2-Azido-4-nitrophenyl)piperidine separated as yellow granules, rapidly becoming scarlet in direct sunlight. The azide was taken up in nitrobenzene and treated as described above. The crude crystalline 5-nitropiperidobenziminazole was washed with light petroleum (b. p. 80—100°), dissolved in boiling dilute hydrochloric acid (charcoal), filtered, and cooled to 10—15°, and the arylamine impurity was diazotised by excess of 2N-sodium nitrite (*ca.* 0·5 c.c.). The solution was poured into ice–aqueous sodium hydroxide containing a little 2-naphthol-3 : 6-disulphonic acid whereby the impurity was removed as water-soluble dye. The solid was collected, dried at 100°, and crystallised from chlorobenzene (200 c.c.), yielding the base (79·8% on amine used), m. p. 218·5—219·5° (very pale yellow leaflets) on further crystallisation from ethyl methyl ketone (Spiegel and Kaufmann, *loc. cit.*, give m. p. 219—220°) (Found : C, 60·8; H, 5·1; N, 19·6. Calc. for $C_{11}H_{11}O_2N_3$: C, 60·9; H, 5·1; N, 19·35%). Spiegel and Kaufmann's " Base A," made as described by them, did not depress this m. p.

5-Aminopiperido(1′ : 2′-1 : 2)*benziminazole*.—The above nitro-compound was reduced in methanol at 50—60° with hydrogen and Raney nickel in a Bergius autoclave; removal of the catalyst and solvent left the base in over 90% yield. The Béchamp method gave lower yields. Crystallised several times from methanol, the *amine*, m. p. 218—220°, was obtained as colourless needles (Found: C, 70·5; H, 7·4; N, 22·5. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%). It was readily soluble in hot water and crystallised with water of crystallisation, the crystals melting at <100°, but the base was extracted from water with chloroform and was anhydrous on removal of the solvent. Boiled with acetic acid–acetic anhydride it yielded an *acetyl* derivative (VI), m. p. 219·5—220° (from chloroform, then ethyl acetate) (Found: C, 68·1; H, 6·7; N, 18·5. $C_{13}H_{15}ON_3$ requires C, 68·2; H, 6·55; N, 18·35%). The amine does not form an aminoazo-compound with diazotised *p*-chloroaniline in dilute acetic acid. The amine was also obtained by acetylating 1-(4-amino-2-nitrophenyl)piperidine (22·1 g., 0·1 mole) for 20 min. with boiling acetic acid (25 c.c.) and acetic anhydride (15 c.c.), the cooled solution poured into excess of ammonia which afforded scarlet 1-(*4-acetamido-2-nitrophenyl*)*piperidine*, m. p. 136—137° (from methanol) (Found: C, 59·8; H, 6·4; N, 16·1. $C_{13}H_{17}O_3N_3$ requires C, 59·5; H, 6·5; N, 16·0%). The latter was reduced at room temperature in methanol with Raney nickel and hydrogen, yielding 1-(*4-acetamido-2-aminophenyl*)*piperidine*, m. p. 132—133° (from ethyl acetate) (Found: C, 67·0; H, 8·1; N, 18·6. $C_{13}H_{19}ON_3$ requires C, 67·0; H, 8·15; N, 18·0%), which couples with diazotised *p*-chloroaniline in sodium acetate solution. The amine (3·5 g.) was diazotised in dilute hydrochloric acid, and the orange diazo-solution added dropwise to sodium azide (2·0 g.) in excess of aqueous 20% sodium acetate; the azido-compound was extracted into nitrobenzene and decomposed as described above; from the concentrated nitrobenzene crystallised 5-acetamidopiperidobenziminazole, m. p. 218—220° (from chlorobenzene), not depressed on admixture of the preceding sample.

6-Aminopiperido(1′ : 2′-1 : 2)*benziminazole*.—5-Acetamidopiperidobenziminazole (5·75 g.) was dissolved in sulphuric acid (*d* 1·84; 30 c.c.) at −10° to −5° with stirring (*ca.* 2 hr.); then at −10° during 15 min. nitric acid (*d* 1·48; 1·1 c.c.) mixed with sulphuric acid (*d* 1·84; 5 c.c.) was added and the temperature was allowed to rise to 0° in 1 hr. The whole was poured on ice, brought to pH 4—5 with aqueous sodium hydroxide (*d* 1·36) with internal ice cooling, then to pH 7—8° with a slurry of sodium carbonate. The yellow precipitate consisted of *5-acetamido-6-nitropiperido*(1′ : 2′-1 : 2)*benziminazole* (5·7 g.), m. p. 199—200° (from ethyl methyl ketone) (Found: C, 56·8; H, 5·9; N, 20·5. $C_{13}H_{14}O_3N_4$ requires C, 57·0; H, 5·1; N, 20·4%). The acetyl group was removed by boiling 2N-hydrochloric acid in 15 min., and the solution was further boiled with charcoal and filtered; on cooling there separated 5-amino-compound hydrochloride, orange leaflets, m. p. 304° (decomp.) with previous sintering. Aqueous sodium carbonate produced the scarlet *base*, m. p. 266—267° (from glycol monoethyl ether) (Found: C, 57·1; H, 5·5; N, 24·2. $C_{11}H_{12}O_2N_4$ requires C, 56·9; H, 5·2; N, 24·1%). The nitroamine (2·45 g.) was dissolved in hydrochloric acid (*d* 1·16; 4 c.c.) and water (6 c.c.) and diazotised at 3—5° with sodium nitrite (0·75 g.) in water (2·5 c.c.); excess of nitrous acid was removed from the filtered solution which was poured into dilute hypophosphorous acid. Nitrogen was rapidly evolved and the temperature rose to 39°; after 30 min. the solution was boiled with carbon, filtered, and basified, yielding *6-nitropiperido*(1′ : 2′-1 : 2)*benziminazole* (1·95 g., 85%), m. p. 217—219° (from methanol) (Found: C, 60·8; H, 5·2; N, 19·70. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1; N, 19·35%). The nitro-group was reduced with hydrogen and Raney nickel in methanol at 60°/5 atm.; removal of catalyst and solvent left colourless crystals of *6-aminopiperido*(1′ : 2′-1 : 2)*benziminazole*, m. p. 198—200° (from ethyl acetate with a little methanol) (Found: C, 70·6; H, 6·9; N, 23·1. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%). The m. p. was not depressed on admixture with the amine obtained by reduction of 6-aminopyridino(1′ : 2′-1 : 2)benziminazole (see below).

7-Aminopiperido(1′ : 2′-1 : 2)*benziminazole*.—1-(2 : 6-Dinitrophenyl)piperidine (Borsche and Rantscheff, *Annalen*, 1911, **379**, 166) was partly reduced in ethanol with aqueous sodium disulphide as described above for 1-(2 : 4-dinitrophenyl)piperidine. Chromatography of the product in benzene removed dark impurities, the yellow eluate was evaporated to dryness, converted into the hydrochloride with ethanol–hydrochloric acid, and diluted with acetone, and the precipitated 1-(*2-amino-6-nitrophenyl*)*piperidine hydrochloride* (80%), m. p. 220—221° (decomp.), was collected and air-dried (Found: Cl^-, 13·6. $C_{11}H_{15}O_2N_3,HCl$ requires Cl^-, 13·8%). The hydrochloride (25·7 g., 0·1 mole) was diazotised in dilute hydrochloric acid and converted into the azide, a dark oil, which was decomposed as described above, but no crystals separated when the nitrobenzene was evaporated to small volume. The nitrobenzene was removed in steam from the acidified (hydrochloric) solution, from which a base (13·3 g.) was

precipitated by pouring the filtered solution into aqueous sodium hydroxide. Adding the base to hot 2N-hydrochloric acid and cooling produced the hydrochloride from which a diazotisable base was removed by washing with acetone. The hydrochloride was again basified, yielding the *nitrobenziminazole* (V), m. p. 107—108°, pale yellow needles [from light petroleum (b. p. 80—100°)] (Found: C, 60·7; H, 5·0; N, 19·3. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·07; N, 19·4%). The crude hydrochloride (9·0 g.), m. p. 258—260° (decomp.), was boiled for 3½ hr. with iron filings (15 g.), acetic acid (15 c.c.), 20% aqueous sodium acetate (15 c.c.), and water (95 c.c.). The black mass was made alkaline, filtered hot, and washed with hot water. Needles (2 g.) separated from the cooled filtrate from which chloroform extracted more base (1·2 g.), whilst 3·3 g. were recovered from the dried iron oxides. The whole was converted into the *7-acetamide*, m. p. 236—237° (from ethanol) (Found: C, 68·2; H, 6·5; N, 18·2. $C_{13}H_{15}ON_3$ requires C, 68·0; H, 6·6; N, 18·4%). Hydrolysis with boiling 2N-hydrochloric acid and basification produced the *amine*, m. p. 186—187° (from benzene) (Found: C, 70·4; H, 7·1; N, 22·4. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%).

Pyrido(1′ : 2′-1 : 2)benziminazole and its derivatives.

Pyrido(1′ : 2′-1 : 2)benziminazole.—Piperido(1′ : 2′-1 : 2)benziminazole (2·0 g.) was carried downwards, during 20 min., in a slow stream of nitrogen or carbon dioxide through palladised charcoal supported on asbestos in a jacketed tube 1 × 35 cm., heated at 306°. The sublimate was extracted with boiling light petroleum (b. p. 60—80°), which removed unchanged piperidobenziminazole, leaving pyrido(1′ : 2′-1 : 2)benziminazole, m. p. 178—179°, pale yellow prisms (from chlorobenzene). Morgan and Stewart (*loc. cit.*) give m. p. 178—179°. With methyl iodide at 100° for 16 hr. it afforded the *methiodide*, m. p. 246—247° (from water) (Found: C, 46·3; H, 3·4; I, 41·6. $C_{12}H_{11}N_3I$ requires C, 46·5; H, 3·55; I, 41·0%).

4-Nitropyrido(1′ : 2′-1 : 2)benziminazole (II).—2-Chloro-1 : 3-dinitrobenzene (58 g., 0·287 mole) (cf. Gunstone and Tucker, *J. Appl. Chem.*, 1952, **2**, 206), 2-aminopyridine (35 g., 0·371 mole), and calcium carbonate (5·0 g.) were boiled under reflux in glycol monoethyl ether (225 c.c.) for 24 hr. Nitrogen oxides were evolved. The mixture was steam-distilled from dilute aqueous hydrochloric acid until chlorodinitrobenzene was removed, and the filtered solution was basified with sodium carbonate. The crude air-dried product (39 g.) was extracted three times with boiling benzene, leaving a yellow insoluble substance (14·3 g.). Chromatography of the benzene solution provided orange *2-(2 : 6-dinitroanilino)pyridine* (I) (14·2 g.), m. p. 117—119° (from methanol) (Found: C, 50·7; H, 3·15. $C_{11}H_8O_4N_4$ requires C, 50·9; H, 3·1%). In ethanol it affords the white *hydrochloride*, sinters at 220—223°, decomp. *ca.* 225°, hydrolysed by water to the free base (Found: Cl^-, 12. $C_{11}H_8O_4N_4$,HCl requires Cl, 11·95%). With methyl iodide at 100° for 7 hr. it afforded the *methiodide*, m. p. 207—208° (decomp.) (crystallised from water; then extracted with ethyl acetate) (Found: C, 36·3; H, 2·6; I, 30·5. $C_{12}H_{11}O_4N_4I$ requires C, 36·0; H, 2·6; I, 31·6%). The above substance insoluble in benzene was extracted with boiling glycol monoethyl ether, and the solution was filtered and cooled yielding *4-nitropyrido(1′ : 2′-1 : 2)-benziminazole* (II) (6·1 g.), m. p. 272°. Evaporation of the solvent to small volume gave a second crop (1·0 g.) (Found: C, 61·9; H, 3·3; N, 19·85. $C_{11}H_7O_2N_3$ requires C, 62·0; H, 3·3; N, 19·75%). The same compound (0·8 g.) was produced by boiling 2-(2 : 6-dinitroanilino)-pyridine (3·0 g.) in glycol monoethyl ether for 16 hr.; nitrous acid was detected in the vapour throughout the period.

4-Aminopyrido(1′ : 2′-1 : 2)benziminazole.—The above nitro-compound (7·1 g.) was reduced by boiling for 3 hr. with iron filings (10·0 g.), water (125 c.c.), and glacial acetic acid (20 c.c.); the mixture was brought to pH 9—10 with aqueous sodium hydroxide, then filtered hot, and the iron oxides were washed with hot water. The filtrate deposited cream-coloured needles (1·7 g.); chloroform extracted more base (4·0 g.) from the dried iron oxides. The *amine* crystallised from benzene in pale yellow needles, m. p. 133—134° (Found: C, 72·0; H, 4·7; N, 23·1. $C_{11}H_9N_3$ requires C, 72·2; H, 4·9; N, 22·9%). With boiling acetic acid–acetic anhydride it gave the acetyl derivative hydrate, m. p. 106—108° (decomp.) (dried in the air), rising to 142—144° on drying at 100° *in vacuo*. Crystallised from acetic anhydride it yielded needles of the *acetyl derivative acetate*, m. p. 147—149° (Found: C, 63·1; H, 5·3; N, 14·5; $C_{15}H_{15}O_3N_3$ requires C, 63·2; H, 5·3; N, 14·7%).

To the amine dissolved in dilute hydrochloric acid was added diazotised *p*-chloroaniline, then aqueous sodium acetate; a scarlet aminoazo-compound was at once precipitated, and crystallised from ethyl methyl ketone as a crimson powder, m. p. 265°. This in turn afforded a yellow diazo-solution, giving a violet pigment with Brenthol OP.

Reduction to 4-*aminopiperidobenziminazole.* In working up the product of reduction of 4-nitropyrido(1′ : 2′-1 : 2)benziminazole with hydrogen and platinum oxide in ethanol there was obtained a fraction, m. p. 170—172°, of lower solubility in methanol which, because it produced a bluish-red pigment on diazotisation and coupling with Brenthol OP, was considered to be probably the above amine. Recrystallised from ethyl acetate it had m. p. 176—177°. 4-Aminopyrido(1′ : 2′-1 : 2)benziminazole (0·8 g.) was therefore reduced in methanol (25 c.c.) with platinum oxide (0·1 g.) at 95°/60 atm. for 3 hr. Removal of catalyst and methanol left a colourless compound, m. p. 176—177° (from ethyl acetate), not depressed with the above amine which must therefore be 4-*aminopiperido*(1′ : 2′-1 : 2)*benziminazole*. The samples were mixed and again crystallised; the m. p. was 177—177·5° (Found: C, 70·4; H, 7·4; N, 22·0. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%).

Nitration. Pyrido(1′ : 2′-1 : 2)benziminazole (2·3 g.) was dissolved with cooling in sulphuric acid (*d* 1·84; 8·0 c.c.), then nitrated during 20 min. with nitric acid (*d* 1·48; 0·6 c.c.) mixed with sulphuric acid (*d* 1·84; 3·0 c.c.), at 10—15°. The whole was stirred for 1 hr., warmed to 40—50° for 15 min., poured into ice-water, and neutralised with ammonia, and the solid collected and dried (3·0 g.; m. p. 260—270°); crystallised from chlorobenzene, then methanol, it formed yellow needles (1·7 g.), m. p. 271—272° (Found: C, 61·8; H, 3·3; N, 19·50. Calc. for $C_{11}H_{17}O_2N_3$: C, 61·9; H, 3·3; N, 19·7%). Morgan and Stewart's 4(6)-nitropyrido(1′ : 2′-1 : 2)benziminazole, prepared as described by them (*loc. cit.*), had m. p. 268—269° (from chlorobenzene, then methanol) (Morgan and Stewart give m. p. 260—262°), not depressed on admixture with the above nitro-compound but depressed with the 4-nitro-isomer. Both samples were reduced with iron filings–acetic acid, and the amines were extracted from the iron oxides with boiling chlorobenzene, as a yellow powder, m. p. and mixed m. p. 230—230·5° (after two crystallisations from ethyl methyl ketone) (Morgan and Stewart give m. p. 229—230°) (Found: C, 72·0; H, 5·0; N, 23·0. Calc. for $C_{11}H_9N_3$: C, 72·2; H, 4·9; N, 22·9%). There can be no doubt that the yellow colour of this amine, commented on by Morgan and Stewart, is inherent and due to its high unsaturation, as is also the case with the 4-isomer. Further the diazo-derivatives of both amines give violet shades on coupling with Brenthol OP and other " red-forming " 2-hydroxynaphthalene-3-carboxyamides. The above amine (0·75 g.) was reduced in methanol (25 c.c.) at 90—100°/50 atm. with platinum oxide and hydrogen for 1 hr.; evaporation of the filtered solution left colourless granules of 6-aminopiperidobenziminazole, m. p. and mixed m. p. 195—197°.

2′ : 3′ : 4′ : 5′ : 6′ : 7′-*Hexahydroazepino*(1′ : 2′-1 : 2)*benziminazole and its derivatives.*

2′ : 3′ : 4′ : 5′ : 6′ : 7′-*Hexahydroazepino*(1′ : 2′-1 : 2)*benziminazole* (VII).—*o*-Chloronitrobenzene (79 g., 0·5 mole) was dissolved in hot butanol (100 c.c.) and to the solution was added hexahydroazepine (hexamethyleneimine) (70 c.c.), then sodium carbonate (3 g.) dissolved in water (15 c.c.), followed by solid sodium carbonate (23·5 g.); the whole was boiled with stirring for 24 hr. The cold solution was filtered, the solids were washed with butanol, and the butanol was removed by heating the filtrate under a vacuum, leaving a yellow oil (97 g., 0·44 mole as 1-*o*-nitrophenyl derivative), $n_D^{23\cdot3}$ 1·601. The oil was reduced with iron filings (150 g.) in boiling ethanol (300 c.c.), hydrochloric acid (*d* 1·16; 15 c.c.) being added in portions; after 18 hr. the solution was made alkaline and filtered, and the iron oxides were washed with hot ethanol which was removed from the filtrate leaving an oil, which was washed with aqueous sodium carbonate and distilled. This yielded 1-*o*-*aminophenylhexahydroazepine* (64 g., 0·336 mole), b. p. 160°/10 mm., $n_D^{23\cdot5}$ 1·564. The base yielded a *monohydrochloride*, m. p. 165—166° (Found: Cl^-, 15·6. $C_{12}H_{18}N_2$,HCl requires Cl^-, 15·65%). The amine (47·5 g., 0·25 mole) was diazotised, converted into the azido-derivative, an oil, which was decomposed in nitrobenzene as described above, and from the concentrated nitrobenzene solution the crude base crystallised (34 g.); more (6 g.) was recovered by extracting the nitrobenzene filtrate with dilute acid. Crystallisation from ethyl methyl ketone, then benzene, yielded the *hexahydroazepinobenziminazole*, m. p. 125—126° (Found: C, 77·6; H, 7·3; N, 15·3. $C_{13}H_{14}N_2$ requires C, 77·4; H, 7·5; N, 15·05%). It formed a *methiodide*, m. p. 232—234° (from water) (Found: C, 48·7; H, 5·4; N, 8·6. $C_{13}H_{17}N_2I$ requires C, 47·6; H, 5·2; N, 8·5%).

5-*Chlorohexahydroazepino*(1′ : 2′-1 : 2)*benziminazole* (VIII).—To 1 : 4-dichloro-2-nitrobenzene (192 g., 1·0 mol.), dissolved in boiling ethanol (300 c.c.), was added dropwise hexahydroazepine (230 c.c.), and the whole was boiled overnight. The ethanol was removed. The residue solidified when washed with dilute hydrochloric acid. It was crystallised from ethanol, yielding the 1-(4-*chloro*-2-*nitrophenyl*) *derivative*, m. p. 56° (Found: C, 56·7; H, 6·2; N, 10·5. $C_{12}H_{14}O_2N_3Cl$ requires C, 56·6; H, 5·9; N, 11·0%). Reduction with iron–ethanol as described

above afforded the **1-(4-chloro-2-aminophenyl)** derivative, b. p. 198—200°/20 mm., n_D^{23} 1·5800, giving a *hydrochloride*, m. p. 200—202° [Found : Cl^-, 13·7%; *M* (titration with $NaNO_2$), 259. $C_{12}H_{17}N_3Cl,HCl$ requires Cl^-, 13·6%; *M*, 261]. This was converted by the steps described above into the *5-chlorobenziminazole derivative* (72% crude), m. p. 107—109° (from ethyl acetate) (Found : C, 65·3; H, 5·8; Cl, 16·0. $C_{12}H_{13}N_2Cl$ requires C, 65·5; H, 5·9; Cl, 16·1%) [*hydrochloride*, sinters at 255°, m. p. 259—261° (Found : Cl^-, 13·2, 13·3. $C_{12}H_{13}N_2Cl,HCl,0·5H_2O$ requires Cl^-, 13·3%); *methiodide*, m. p. 273—274° (Found : C, 43·2; H, 4·6; I, 34·0. $C_{13}H_{16}N_2ClI$ requires C, 43·0; H, 4·4; I, 35·0%)].

Passing a slow stream of chlorine into a solution of the base (2·2 g.) in chloroform (15 c.c.) at 0° gave a precipitate (2·4 g.), m. p. 314° (decomp.), of a *dichloride* (Found : C, 50·7; H, 4·4; Cl, 36·4. $C_{12}H_{13}N_2Cl_3$ requires C, 49·4; H, 4·5; Cl, 36·5%). A few grains placed on starch–iodide paper moistened with sodium carbonate left a blue mark; chlorine was evolved on treatment with warm dilute hydrochloric acid. The compound reacted with boiling water and a base was precipitated on addition of sodium carbonate to the cool solution. Apparently self-chlorination occurred in the aromatic ring producing the 5 : x-*dichlorobenziminazole*, m. p. 176—177° (thrice crystallised from ethyl acetate) (Found : C, 57·2; H, 5·1; Cl, 27·4. $C_{12}H_{12}N_2Cl_2$ requires C, 56·5; H, 4·7; Cl, 27·8%). No chlorine was removed from the last compound by boiling aqueous sodium hydroxide or alcoholic potassium hydroxide. Sundry piperidino- and hexahydroazepino-benziminazoles were similarly treated with chlorine or bromine and invariably a precipitate containing loosely-held halogen was formed, but no systematic study of the substances was made. The residue (1·3 g.) left on removal of the chloroform had not the above properties but was not unchanged starting material and it had an odour not unlike that of chloral; it was not further examined.

Hexahydro-5-nitroazepino(1′ : 2′-1 : 2)benziminazole (IX).—To 1-chloro-2 : 4-dinitrobenzene (202 g., 1·0 mol.) in boiling ethanol (300 c.c.) was added dropwise hexahydroazepine (230 c.c.), and the whole was boiled overnight, then cooled, and the orange cake was collected and washed with water. Crystallisation from methanol, then light petroleum (b. p. 80—100°), yielded the 2 : 4-*dinitrophenyl derivative*, m. p. 108—109°, yellow leaflets (Found : C, 54·3; H, 5·9; N, 15·8. $C_{12}H_{15}O_4N_3$ requires C, 54·3; H, 5·7; N, 15·8%). To the damp cake (91—92% yield) dissolved in boiling ethanol (0·8—1·0 l.) was added during 3 hr. a solution of sodium disulphide prepared from hydrated sodium sulphide (240 g.) and sulphur (32 g.) in water (500 c.c.), and the whole was boiled overnight and the ethanol removed. The residue was taken up in benzene (700 c.c.), washed with cold water until the washings were pale yellow, and filtered, and the benzene was removed. To the residue was added hydrochloric acid (*d* 1·16), and the resultant solid hydrochlorides were collected and washed with a little hydrochloric acid. Basification of the filtrate produced **1-(4-*amino*-2-*nitrophenyl*)*hexahydroazepine***, m. p. 76—77°, dark purple needles [from light petroleum (b. p. 80—100°)] (Found : C, 61·2; H, 7·5; N, 17·5. $C_{12}H_{17}O_2N_3$ requires C, 61·2; H, 7·2; N, 17·9%). The filter cake was washed in water (1 l.) which leached out a little more of the above compound; then it was dissolved in boiling methanol (1 l.), basified with methanolic potassium hydroxide, treated with charcoal, filtered, and cooled, whereupon **1-(2-*amino*-4-*nitrophenyl*)*hexahydroazepine*** crystallised. It was collected, dried, dissolved in benzene, and filtered through active alumina (6 × 2·5 cm.) which retained a black substance; the base (94·0 g., 0·4 mol.) crystallised in large orange prisms. A sample (21·4 g.) was distilled in a short-path still at 172·8—173·5°/0·15 mm. and the first fraction (8·1 g.) proved to be the pure base, m. p. 67—68·5° (Found : C, 61·2; H, 7·5; N, 17·7. $C_{12}H_{17}O_2N_3$ requires C, 61·2; H, 7·2; N, 17·85%). As described for the piperidine analogue the above base was converted *via* the azido-derivative into *hexahydro-5-nitroazepino(1′ : 2′-1 : 2)benziminazole*, m. p. 174—175° (from chlorobenzene) (Found : C, 62·3; H, 5·7; N, 18·0. $C_{12}H_{15}O_2N_3$ requires C, 62·3; H, 5·63; N, 18·1%), reduced with hydrogen and Raney nickel in methanol at 50—55°/30 atm. to the *amine* (X), m. p. 180·5—181°, obtained free from a pink impurity after five crystallisations from methanol (Found : C, 71·8; H, 7·3; N, 21·0. $C_{12}H_{15}N_3$ requires C, 71·7; H, 7·5; N, 20·9%). Boiled with acetic acid–acetic anhydride the amine afforded the *acetyl* derivative, m. p. 254—255° (from glycol monoethyl ether) (Found : C, 68·9; H, 7·1; N, 17·1. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%). The amine (6 g.), dissolved in methanol (15 c.c.) and poured into water (150 c.c.), afforded a clear solution which, when shaken with excess of ethyl chloroformate with portionwise addition of aqueous sodium hydroxide to pH 10, afforded the *ethoxycarbonyl derivative* (8·1 g.), m. p. 238—240° (from methanol) (Found : C, 66·1; H, 6·6; N, 15·3. $C_{15}H_{19}O_2N_3$ requires C, 66·0; H, 6·98; N, 15·35%), which with methyl iodide at 100° (17 hr.) yielded *5-ethoxycarbonylaminohexahydro-1-methylazepino(1′ : 2′-1 : 2)benziminazolinium iodide*, m. p. 270—272° (decomp.) (Found : C, 46·2; H, 5·3.

$C_{16}H_{23}O_2N_5I$ requires C, 46·3; H, 5·3%). The amine was condensed with 2-hydroxy-3-naphthoic acid in boiling toluene with phosphorus trichloride and worked up by steam-distillation from aqueous sodium hydroxide and precipitation with sodium hydrogen carbonate, providing *hexahydro-5-(2-hydroxy-3-naphthamido)azepino*(1′ : 2′-1 : 2)*benziminazole*, m. p. 310—311° (from ethylene glycol) (Found: C, 74·0; H, 5·8; N, 11·6. $C_{23}H_{21}O_2N_3$ requires C, 74·5; H, 5·6; N, 11·3%). To the amine (4·0 g.) dissolved in hot water (100 c.c.) with 2N-hydrochloric acid (10 c.c.) was added 2-amino-4-chloro-6-methylpyrimidine 1-methiodide, (5·7 g.) dissolved in boiling water (100 c.c.), followed by aqueous sodium acetate added dropwise to remove hydrochloric acid as liberated; after 7 min. the solution was filtered and treated with sodium iodide to precipitate *2-amino-4-[hexahydroazepino*(1′ : 2′-1 : 2)*benziminazol-5-ylamino]-1 : 6-dimethylpyrimidinium 1-iodide*, m. p. *ca.* 220° (rapid heating) (from methanol) (Found: C, 47·3; H, 5·1; N, 18·7. $C_{15}H_{23}N_6I$ requires C, 48·0; H, 5·1; N, 18·6%). This compound with methyl iodide at 100° (17 hr.) afforded the *trimethyl compound di-iodide*, m. p. 335° (from water) (Found: C, 37·5; H, 4·3. $C_{19}H_{26}N_6I_2H_2O$ requires C, 37·4; H, 4·6%). To the amine (8·0 g.) in boiling benzene was added adipoyl chloride (3·0 c.c.) in benzene and the resultant thick mass was further diluted with benzene. After cooling, the solid was collected, basified, and boiled with methanol, yielding *NN′*-di(hexahydroazepinobenziminazol-5-yl)adipamide, m. p. 345° (decomp.) (from glycol), quaternised as above to the *1 : 1′-dimethyl compound 1 : 1′-di-iodide*, m. p. 345° (decomp.) (from water) (Found: C, 49·0; H, 5·4; $C_{32}H_{42}O_2N_6I_2$ requires C, 48·2; H, 5·3%). Passing carbonyl chloride into a solution of the base in warm water produced a thick precipitate which was collected, dissolved in boiling water, and poured into aqueous ammonia, yielding the urea, m. p. 335°, as colourless leaflets (from glycol), quaternised by heating with methyl toluene-*p*-sulphonate at 120°, rising to 160° during 2 hr., cooling, washing with ether, dissolution in boiling water, and addition of sodium iodide to *di(hexahydro-1-methylazepinobenziminazol-5-yl)-urea di-iodide*, m. p. 316—318° (decomp.) (from water) (Found: C, 45·0; H, 4·7; I, 34·6. $C_{27}H_{34}ON_6I_2$ requires C, 45·5; H, 4·8; I, 35·7%).

Hexahydro-5-hydroxyazepino(1′ : 2′-1 : 2)*benziminazole*.—The orange diazonium salt derived from the 5-amino-compound is very stable to heat. The amine (8·0 g.) was diazotised in phosphoric acid (20 c.c.) and water (40 c.c.), and the diazo-solution was added dropwise during 40 min. to phosphoric acid (60 c.c.) stirred and heated in a graphite bath at 130—140°; after 75 min. the diazo-reaction had become weak and the cooled solution was poured into water (*ca.* 400 c.c.). The pH was brought to 7—7·5 with 33% aqueous sodium hydroxide (120 c.c.) which precipitated most of the product as brown flakes. These were collected and dissolved in boiling water (150 c.c.) with 2N-hydrochloric acid (20 c.c.), and the solution was dropped into excess of boiling 2N-sodium carbonate, yielding at first a dark gum which was discarded, then cream-coloured granules. The latter were dissolved in dilute sodium hydroxide solution, and from the filtered solution sodium hydrogen carbonate precipitated the *phenol* (1·6 g.), m. p. 295—296° (from methanol) (Found: C, 71·2; H, 7·2. $C_{13}H_{14}ON_2$ requires C, 71·3; H, 6·9%).

6-Aminohexahydroazepino(1′ : 2′-1 : 2)*benziminazole* (XIII).—5-Acetamidohexahydroazepinobenziminazole (13·2 g.) was dissolved during 2 hr. with stirring in cold sulphuric acid (*d* 1·84; 100 c.c.) at −10° to −5° and nitrated at that temperature with nitric acid (*d* 1·4; 2·4 c.c.) in sulphuric acid (*d* 1·84; 10 c.c.) added during 15 min.; after a further 15 min. the whole was poured on ice. A sample poured on ice and aqueous sodium hydroxide yielded yellow *5-acetamidohexahydro-6-nitroazepino*(1′ : 2′-1 : 2)*benziminazole*, m. p. 190—191° (from ethyl methyl ketone, then chlorobenzene) (Found: C, 58·8; H, 5·9; N, 19·0. $C_{14}H_{16}O_3N_4$ requires C, 58·4; H, 5·6; N, 19·4%). The remainder was hydrolysed by boiling the acid solution for 5 min., cooling, and pouring on ice and aqueous sodium hydroxide (sufficient to bring the pH to 7—8), the scarlet *5-amino-6-nitro-base* (XI) being precipitated; it had m. p. 295—296° (decomp.) (from glycol monoethyl ether, then sublimed at 185°/0·003 mm.) (Found: C, 58·3; H, 5·7. $C_{12}H_{14}O_2N_4$ requires C, 58·5; H, 5·7%). The nitro-amine (4·9 g.) was deaminated by diazotisation and treatment with hypophosphorous acid, yielding *hexahydro-6-nitroazepino*(1′ : 2′-1 : 2)-*benziminazole* (XII) (2·1 g.), m. p. 196—197° (after sublimation at <170°/0·003 mm., then chromatography on alumina from benzene and development with benzene–chloroform and finally crystallisation from ethyl acetate) (Found: C, 62·3; H, 5·7; N, 18·3. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·63; N, 18·1%). Reduction of this compound (1·0 g.) by hydrogen with Raney nickel in methanol at 50°/50 atm. yielded the *amine* (XIII) (0·86 g.), m. p. 198—199° (from benzene) (Found: C, 71·9; H, 7·6; N, 21·0. $C_{12}H_{15}N_3$ requires C, 71·7; H, 7·5; N, 20·9%).

Hexahydro-1-(2-amino-6-nitrophenyl)azepine.—To 2-chloro-1 : 3-dinitrobenzene (50 g.) in boiling ethanol (250 c.c.) was added dropwise hexahydroazepine (57·0 c.c.), and the whole was

boiled for 6 hr., then cooled. The separated solid (16 g.) was collected and washed with water; evaporation to small bulk produced a further 8·0 g. Removal of the solvent left a neutral oil which could not be crystallised either before or after chromatography in benzene on alumina. The mixed solids, when crystallised from light petroleum (b. p. 80—100°) and then from methanol, yielded the 2 : 6-*dinitrophenyl derivative*, m. p. 73—74° (Found: C, 54·2; H, 6·0; N, 15·2. $C_{12}H_{15}O_4N_3$ requires C, 54·3; H, 5·7; N, 15·8%). This (20 g.) was reduced in boiling ethanol (200 c.c.) with sodium disulphide [from sodium sulphide nonahydrate (18·2 g.) and sulphur (2·42 g.)] added during 3 hr., and the whole boiled for 20 hr. That part of the product soluble in benzene was chromatographed on alumina, giving a yellow bottom band, an orange main band, and a narrow dark band at the top. The orange band afforded red needles which melted at room temperature but when set aside and scratched afforded an orange form of the 2-*amino*-6-*nitrophenyl derivative*, m. p. 56—57° [from light petroleum (b. p. 80—100°)] (Found: C, 61·2; H, 7·4; N, 17·7. $C_{12}H_{17}O_2N_3$ requires C, 61·2; H, 7·2; N, 17·9%).

Other benziminazoles.

5-*Chloromorpholino*(4′ : 3′-1 : 2)*benziminazole* (XIV).—4-(4-Chloro-2-nitrophenyl)morpholine (Harradence and Lions, *J. Proc. Roy. Soc. N.S.W.*, 1937, **70**, 406) was reduced with neutral iron filings in ethanol to 4-(2-*amino*-4-*chlorophenyl*)*morpholine* (81%), m. p. 135—137° (from methanol) (Found: C, 56·8; H, 6·1; N, 13·0. $C_{10}H_{13}ON_2Cl$ requires C, 56·6; H, 6·1; N, 13·2%). Diazotisation produced a clear brown-yellow solution which on interaction with sodium azide afforded a grey granular azido-compound, m. p. 80—81° (decomp.; slow heating). The azide was decomposed in nitrobenzene and after concentration the crystalline material was collected and converted into 5-*chloromorpholino*(4′ : 3′-1 : 2)*benziminazole hydrochloride*, m. p. 228—230° (from methanol) (Found: Cl^-, 14·3. $C_{10}H_9ON_2Cl,HCl$ requires Cl^-, 14·5%), from which was obtained the free *base* (XIV), m. p. 200—200·5° (from ethyl acetate) (Found: C, 57·2; H, 4·2; N, 13·1. $C_{10}H_9ON_2Cl$ requires C, 57·6; H, 4·3; N, 13·4%). At 100° the base formed a *methiodide*, m. p. 242—244° (decomp.) (from water, then washed with acetone) (Found: I, 35·9. $C_{11}H_{12}ON_2ClI$ requires I, 36·2%). As the yield of crude base was only 50% the nitrobenzene was removed from the filtrate by steam-distillation from dilute hydrochloric acid, from which after cooling and filtering sodium carbonate liberated a mixture of bases, m. p. <100°. Chromatography on alumina from benzene afforded the base (XIV) in the first eluate, after which the m. p. fell and by again chromatographing the later eluates there was obtained a *base*, m. p. 100—100·5° (Found: C, 54·7; H, 4·5; Cl, 18·7%). It afforded a picrate, m. p. 230—232°, was not diazotisable and occurred in every preparation of (XIV) but it was not further investigated.

Nitration. The base (XIV) (9·0 g.) was dissolved in sulphuric acid (*d* 1·84; 50 c.c.) and nitrated at 10—15° during 10 min. with nitric acid (*d* 1·48; 1·85 c.c.) mixed with sulphuric acid (*d* 1·84; 6·0 c.c.); after ½ hr. the solution was warmed to 40°, then poured on ice and brought to pH 10—11 with aqueous sodium hydroxide and the insoluble material was collected from the cooled solution. By fractional crystallisation from chlorobenzene were obtained colourless needles (7·2 g.) of a *nitro-compound*, m. p. 219—220° (Found: C, 47·0; H, 3·1; N, 16·1. $C_{10}H_8O_3N_3Cl$ requires C, 47·3; H, 3·1; N, 16·6%). The latter was reduced with Raney nickel and hydrogen at 60—65°/100 atm. in methanol; crystals separated from the cold methanol and were removed from the nickel with hot methanol, producing x-*amino*-5-*chloromorpholino*-(4′ : 3′-1 : 2)*benziminazole*, m. p. 262—263°, as colourless needles (Found: C, 53·8; H, 5·3; N, 19·2. $C_{10}H_{10}ON_3Cl$ requires C, 53·8; H, 4·5; N, 18·8%). The base does not form an aminoazo-compound with diazotised *p*-chloroaniline in dilute acetic acid. The original nitro-compound must have been a eutectic mixture of three isomers since by evaporating the methanol filtrates there were obtained two crude bases, one, m. p. 218—235°, soluble in hot chlorobenzene, the other, m. p. 218—240°, insoluble in chlorobenzene. Both these bases afforded aminoazo-compounds with diazotised *p*-chloroaniline.

Partial Reduction of 4-(2 : 4-*Dinitrophenyl*)*morpholine.*—4-(2 : 4-Dinitrophenyl)morpholine (Harradence and Lions, *loc. cit.*) was reduced with sodium disulphide as described above for the piperidine analogue, and the product was chromatographed on alumina from benzene, giving an upper red and lower yellow fraction. Neither of these yielded pure compounds and better separation resulted by utilisation of their difference in basicity or the solubility of their hydrochlorides. Treatment of either fraction with aqueous hydrochloric acid (*d* 1·16) yielded a sparingly soluble hydrochloride of the yellow isomer, freed by basification, as was the red isomer from the filtrate. Each fraction was then further purified by dissolution in 0·5*N*-hydrochloric acid to which aqueous sodium acetate was added to pH 2—3, whereupon the yellow base

separated; at pH 4—5 a mixture separated and at pH 6—7 the red base. Alternatively, the mixture was dissolved in aqueous acetic acid and hydrochloric acid added to pH 3—4: the yellow base crystallised, leaving nearly pure red base in solution. The yellow base, since its diazo-derivative afforded a red pigment with Brunthol OP, was probably 4-(2-*amino*-4-*nitrophenyl*)*morpholine*; it had m. p. 153—153·5° (from methanol) (Found: C, 53·7; H, 6·2; N, 18·4. $C_{10}H_{13}O_3N_3$ requires C, 53·8; H, 5·85; N, 18·85%). The red base was probably 4-(4-*amino*-2-*nitrophenyl*)*morpholine* and had m. p. 133—135° (from ethyl acetate) (Found: C, 54·1; H, 5·4; N, 19·1%); its diazo-derivative afforded a purple pigment with Brenthol OP, typical of a *NN*-dialkyl *p*-diamine.

4′-*N*-*Ethoxycarbonylpiperazino*(1′ : 2′-1 : 2)*benziminazole* (XV).—1-Ethoxycarbonylpiperazine (18 g.) was boiled in ethanol (20 c.c.) with *o*-chloronitrobenzene (9·0 g.) for 48 hr., the ethanol was removed, and the residual oil poured into water and extracted with benzene. Removal of the benzene left a mobile orange oil, n_D^{20} 1·553. Chromatography of a sample from benzene over alumina gave a single fast-moving orange band, and evaporation of the eluate left an orange oil, n_D^{20} 1·557. The oil (13·3 g.) was reduced with neutral iron in ethanol, giving an oil which crystallised. The crystals were taken up in chloroform, the solution filtered, and the solvent removed, leaving crude amine (10·9 g.) which was crystallised from light petroleum affording 1-2-*aminophenyl*-4-*ethoxycarbonylpiperazine*, m. p. 109·5—110° (Found: C, 62·5; H, 7·9; N, 16·8. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·6; N, 16·9%). The amine (5·0 g.) was dissolved in warm water (44 c.c.) and hydrochloric acid (*d* 1·16; 6·0 c.c.); on cooling, the hydrochloride separated [m. p. 240° (decomp.)] and was diazotised to a deep yellow-brown solution which on interaction with sodium azide produced a brown oil. The latter was taken up in nitrobenzene, and decomposed at 170—180°, and the solution concentrated *in vacuo*. Aniline was found in the distillate. As no solid separated from the residue it was extracted with dilute hydrochloric acid; addition of aqueous sodium acetate gave a black precipitate which was removed, and from the filtrate aqueous ammonia liberated a base which was extracted into benzene and chromatographed on alumina, giving, from the bottom up, a small yellow band, a long pale yellow zone, a small pale orange, and a small black band. The benzene eluate of the pale yellow zone yielded a yellow oil (0·25 g.), giving a solid, m. p. 124—125°, from ethyl acetate. Drying and extraction of the yellow zone with methanol also gave an oil (0·55 g.), giving a solid, m. p. 124—125°, from ethyl acetate. Addition of picric acid to the filtrates gave a picrate, m. p. 216—218° (decomp.); this was collected and decomposed with dilute aqueous sodium hydroxide, and the base taken into benzene which was then removed; the residue, crystallised from ethyl acetate, had m. p. 126—127°. Mixed m. p.s having shown all samples to be identical they were mixed and crystallised from ethyl acetate, yielding 4′-*ethoxycarbonylpiperazino*(1′ : 2′-1 : 2)-*benziminazole* (XV) (0·3 g.), m. p. 126—127° (Found: C, 63·4; H, 6·6; N, 16·8. $C_{13}H_{15}O_2N_3$ requires C, 63·8; H, 6·1; N, 17·1%).

5-*Chloro*-4′-*ethoxycarbonylpiperazino*(1′ : 2′-1 : 2)*benziminazole* (XVI).—1-Ethoxycarbonylpiperazine (12·1 g.), 1 : 4-dichloro-2-nitrobenzene (7·35 g.), and ethanol (25 c.c.) were heated on the steam-bath for 20 hr., the ethanol was removed, and the orange gum treated with water and extracted with benzene which on evaporation left an orange oil. This was reduced directly with iron in aqueous acetic acid. The cold mixture was filtered and the iron oxides were dried; both filtrate and oxides were extracted with chloroform, which on evaporation and crystallisation of the residues from light petroleum (b. p. 80—100°), then from ethyl acetate, yielded colourless granules of 1-(2-*amino*-4-*chlorophenyl*)-4-*ethoxycarbonylpiperazine*, m. p. 119—120° (Found: C, 55·2; H, 6·6; N, 14·8. $C_{13}H_{18}O_2N_3Cl$ requires C, 55·0; H, 6·35; N, 14·8%). Diazotisation (7·8 g.) and reaction with sodium azide produced a pinkish solid azido-derivative which was collected, dissolved in nitrobenzene, and decomposed. The basic products were extracted with dilute hydrochloric acid, recovered by basification, taken up into ethyl acetate, and converted into the picrate (4·8 g.). This was decomposed with dilute aqueous sodium hydroxide. Then benzene-extraction yielded crude base (2·2 g.), m. p. 109—119°. On chromatography from benzene on alumina the first eluate afforded the *base* (XVI), m. p. 129—131° (from ethyl acetate) (Found: C, 56·3; H, 5·2; N, 14·8. $C_{13}H_{14}O_2N_3Cl$ requires C, 55·9; H, 5·0; N, 15·0%).

1-*Amino*-5-*nitro*-2 : 4-*dipiperidinobenzene* (XVIII).—To a solution of piperidine (40 c.c.) in boiling ethanol (150 c.c.) was added with stirring during 30 min. 2 : 4-dichloro-1 : 5-dinitrobenzene (11·85 g.), and the whole was boiled for 1 hr. and cooled; the yellow crystals were collected, washed with water, and dried (91%; m. p. 116—117°). The compound contained no chlorine. A sample, crystallised from glacial acetic acid, yielded 1 : 5-dinitro-2 : 4-dipiperidinobenzene, m. p. 117—118° (Found: C, 57·7; H, 5·6; N, 16·9. Calc. for $C_{16}H_{22}O_4N_4$: C, 57·5; H, 6·6; N, 16·8%) (Le Fèvre and Turner, *J.*, 1927, 1118, give m. p. 130—131°). The latter

(87 g.) was reduced in boiling ethanol with sodium disulphide [from sodium sulphide nonahydrate (62·5 g.) and sulphur (8·35 g.)] added during 20 min., and the whole was boiled overnight; the ethanol was removed, and water was added to the residue which was then extracted with benzene and washed with cold water until the washings were pale yellow. The benzene solution was filtered, dried (Na_2SO_4), and taken to dryness; the residue crystallised, was collected, washed with ethanol at 3—5°, and air-dried (43 g.). The solid was dissolved in 2N-hydrochloric acid (300 c.c.) and filtered from unchanged dinitro-compound (3·7 g.), and the filtrate was poured slowly into boiling dilute aqueous sodium hydroxide; an oil was precipitated which crystallised in deep crimson granules and there was collected from the hot solution the *base* (XVIII) (37·0 g.), m. p. 129—130° not altered by crystallisation from ethyl acetate (Found: C, 63·4; H, 8·3; N, 18·6. $C_{16}H_{24}O_2N_4$ requires C, 63·2; H, 7·9; N, 18·6. $C_{16}H_{24}O_2N_4$ requires C, 63·2; H, 7·9; N, 18·4%).

5-Amino-6-piperidinopiperido(1′ : 2′-1 : 2)benziminazole (XIX).—Diazotisation of the above base (21·2 g.) afforded the deep orange-brown diazo-solution which, added to sodium azide in aqueous sodium acetate, gave a tarry azide. A crystalline form was obtained by adding sodium acetate to the diazo-solution, followed by sodium azide. Either form dissolved in nitrobenzene and, when heated to 120—130°, evolved not only nitrogen but also nitrogen oxides; heating was continued to 170—180°, the nitrobenzene was reduced to small volume *in vacuo*, and the residue was extracted with diluted hydrochloric acid, boiled to remove nitrobenzene, and basified with sodium carbonate. The dry crude product was extracted with boiling light petroleum (b. p. 80—100°) (*ca.* 250 c.c.), from which crystallised an orange substance (*ca.* 1·0 g.), m. p. 100—110°. The insoluble portion was dissolved in benzene and chromatographed on alumina, yielding a large orange fraction which on evaporation provided a sticky orange base (8·5 g.) converted by ethanolic hydrochloric acid into a hydrochloride (7·1 g.), decomp. 240° (after washing with cold acetone). The hydrochloride on basification yielded an orange-red mass (5·1 g.) consisting of orange and red crystals which proved to be two forms of *5-nitro-6-piperidinopiperido(1′ : 2′-1 : 2)benziminazole* (XIX), scarlet needles, m. p. 137—140°, resolidifying to an orange form, m. p. 155—156° (Found: C, 63·9; H, 7·8; N, 19·0. $C_{16}H_{20}O_2N_4$ requires C, 64·0; H, 6·66; N, 18·66%). Slow evaporation *in vacuo* at room temperature of the substance in ethyl methyl ketone solution yielded the red needles; quick crystallisation from a concentrated solution in the ketone gave both forms; a less concentrated solution gave the red needles first (removed from the warm solution), then orange plates from the filtrate evaporated *in vacuo*. Reduction in methanol with Raney nickel and hydrogen at 50—55°/50 atm. yielded the *amine* (XX), which had m. p. 189—191° after sublimation *in vacuo*, chromatography on alumina from benzene, development with benzene–chloroform, and crystallisation from ethyl acetate (Found: C, 71·1; H, 8·0; N, 21·1. $C_{16}H_{22}N_4$ requires C, 71·1; H, 8·2; N, 20·7%).

Di[piperido(1′ : 2′-1 : 2)glyoxalino](4′ : 5′-1 : 2)(5″ : 4″-4 : 5)benzene (XXI).—The above amine (1·7 g.) in dilute hydrochloric acid was diazotised, yielding a reddish-orange solution which, added with stirring to sodium azide in aqueous sodium acetate, produced the azido-derivative as pale pink granules. These were heated in nitrobenzene and worked up as described above. Basification of the hydrochloric acid solution produced a dark sticky mass from which the liquid was decanted. From this liquid were slowly deposited purple leaflets which, twice crystallised from ethyl methyl ketone, yielded pinkish needles of a strong base, m. p. 284—287°. After 2 more days the liquid deposited a further crop (0·3 g.) from which at 245°/0·003 mm. was obtained a colourless sublimate of the *base* (XXI), m. p. 279—280° (Found: C, 72·0; H, 7·0; N, 21·3. $C_{16}H_{18}N_4$ requires C, 72·2; H, 6·8; N, 21·0%). The residue from the sublimation was a fluffy purple mass, m. p. >300° after sintering.

2 : 4-Dinitro-1 : 5-di-(2-pyridylamino)benzene.—2 : 4-Dichloro-1 : 5-dinitrobenzene (9·6 g.) and 2-aminopyridine (16·0 g.) were boiled in glycol monoethyl ether (60 c.c.) for 24 hr. No nitrous oxide was evolved. Solid began to separate during boiling and, on cooling, the mass set solid. The solid was collected, washed with more solvent, then water, and dried, yielding the *base* (10·3 g.), m. p. 236—238° (from chlorobenzene) (Found: C, 54·3; H, 3·9; N, 23·4. $C_{16}H_{12}O_4N_6$ requires C, 54·6; H, 3·4; N, 23·8%).

Attempts to condense 2 : 4-dichloro-1 : 5-dinitrobenzene with hexahydroazepine under the conditions used for piperidine led to a compound which did not give correct analyses for the expected product and afforded no nitro-amine on reduction with sodium disulphide.

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Autoxidation of αβ-Unsaturated Ketones.

By E. G. E. Hawkins.

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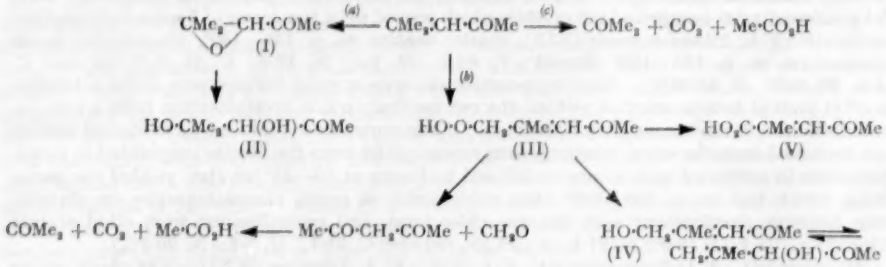
Oxidation of mesityl oxide and *iso*phorone led to products of types similar to those derived from oxidation of alkenes and *cyclo*alkenes. Mesityl oxide gives the epoxide and β-acetyl-α-methylacrylic acid, and *iso*phorone yields largely 5 : 5-dimethyl-3-oxo*cyclo*hexene-1-carboxylic acid.

The products of autoxidation of olefins have been studied in detail (Gasson, Millidge, Primavesi, Webster, and Young, *J.*, **1954**, **2161**, and unpublished work). They were mainly derived (*a*) by reaction at the double bond *via* epoxides, (*b*) by attack at the active methylene group *via* hydroperoxides, and (*c*) by fission at the double bond. Oxidation of two αβ-unsaturated ketones, mesityl oxide and *iso*phorone, has now been studied to find what modifying effect the carbonyl group has on the mode of reaction.

Autoxidation of mesityl oxide in acetic acid had previously been found to lead to β-acetyl-α-methylacrylic acid (Distillers Co. Ltd., Elce, Hall, and Turck, B.P. 585,527), and this acid was also found in the present work in the products obtained under neutral conditions. A major product, however, was the epoxide (I), and other products were carbon dioxide, formaldehyde, acetaldehyde, acetic acid, acetone, and 3 : 4-dihydroxy-4-methylpentan-2-one (II) : in addition there were present esters of this glycol with formic acid



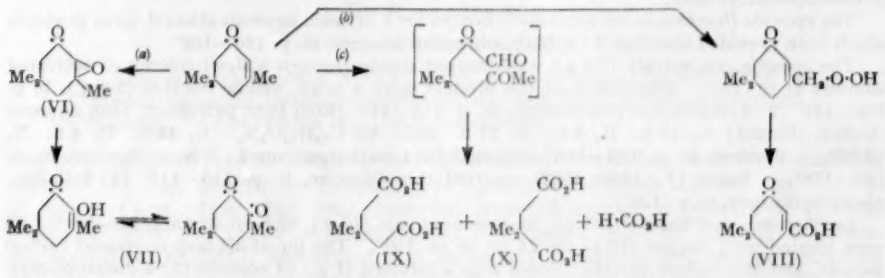
and α-methyl-β-acetylacrylic acid (V), and an unidentified compound containing hydroxyl, carbonyl, and unsaturated functions, cleaved by periodic acid, possibly 3-hydroxy-4-methylpent-4-en-2-one (IV). The annexed diagram represents possible stages of oxidation. These products indicate that the oxidation proceeds similarly to that of olefins.

Nicolet and Poulter's method of epoxide estimation (*J. Amer. Chem. Soc.*, 1930, **52**, 1186) was not applicable in this work since the mesityl oxide itself reacted with hydrogen chloride under the conditions used. A modified periodate method, with more concentrated acid or a higher temperature than normal, gave reasonably accurate analyses.

The epoxide was easily hydrolysed to the corresponding glycol, and when passed through activated alumina at *ca.* 250° gave poor conversion into 4-methylpentan-2 : 3-dione. This epoxide had previously been formed only by oxidation of mesityl oxide by alkaline hydrogen peroxide (Weitz and Scheffer, *Ber.*, 1921, **54**, 2327; Bunton and Minkoff, *J.*, 1949, 665; Nazarov and Akhren, *J. Gen. Chem., U.S.S.R.*, 1950, **20**, 2183; Publicker Commercial Alcohol Corp., U.S.P. 2,431,718). The Russian workers also hydrolysed it to the glycol.

Autoxidation of *iso*phorone in alcoholic alkali has been described as slow by Treibs (*Ber.*, 1933, **66**, 1483), and the unsaturated ketol (VII), similar to that produced from the epoxide by alkali treatment, was apparently the only compound identified. Oxidation of some related *cyclo*alkenones was studied in greater detail (Treibs, *Ber.*, 1930, **63**, 2423; 1932, **65**, 163; 1933, **66**, 610), and the products were assumed to arise *via* the epoxides. It has now been found that autoxidation of *iso*phorone is slower than that of mesityl oxide,

but gave mainly acidic materials with little epoxide—none was isolated. The main products were αα-dimethylsuccinic acid (X), ββ-dimethylglutaric acid (IX), and a compound thought to be 5:5-dimethyl-3-oxo*cyclo*hex-1-enecarboxylic acid (VIII); small



quantities of carbon dioxide, acetone, and acetic acid were also found. In addition, derivatives of a diketone, presumably Treibs's ketol formed by isomerisation of the epoxide, were obtained from a high-boiling fraction. Oxidation was thought to follow the annexed scheme. Ozonolysis of the acid (VIII), followed by decomposition of the ozonide in acetic acid and hydrogen peroxide, yielded ββ-dimethylglutaric acid (IX). Analysis of the acid and its carbonyl derivatives, together with the above ozonolysis, agree with the suggested structure.

The products of oxidation again provided evidence of the three modes of attack, and the low yields of epoxide (VI) might have been due to (i) its rapid rearrangement to the ketol (VII) or conversion into glycol, or (ii) predominance of oxidation type (*b*) as is found with *cyclo*alkenes (unpublished work).

Experimental

The method of oxidation and apparatus are described by Gasson *et al.* and by Hawkins and Quin (unpublished work).

Mesityl Oxide.—Oxidations were carried out with and without metal naphthenate catalysts and basic additives, and at temperatures from 70° to 110°. The rate of oxidation was increased by the metal catalysts, decreased slightly by magnesium oxide, and decreased considerably by sodium carbonate or hydroxide. In one typical experiment, mesityl oxide (137 g.), containing cobalt naphthenate (0·1 g.), was treated with dried oxygen at *ca.* 100° for 9¼ hr. The total oxygen absorbed was 17 l., and carbon dioxide (3·3 l.) was isolated from the liquid-air trap at the end of the experiment. From a solid carbon dioxide–alcohol trap was obtained a liquid (3·9 g.) consisting of acetone (2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 124—126°) and acetaldehyde (dimedone derivative, m. p. and mixed m. p. 139—140°). Part (71 g.) of the main liquid product (143·7 g.) was distilled to give fractions: (i) (2·7 g.), b. p. 100—126°; (ii) (36·5 g.), b. p. 126—134°; (iii) (1·2 g.), b. p. 134—150°; (iv) (8·5 g.), b. p. 150—160° (mainly 155°); (v) (2·4 g.), b. p. 64—80°/15 mm.; (vi) (3·8 g.), b. p. 80—110°/15 mm.; (vii) (5·0 g.), b. p. 110—140°/15 mm.; residue (2·8 g.). Fraction (i) contained acetic acid (*p*-bromophenacyl ester, m. p. and mixed m. p. 84—86°). Fraction (ii) was unchanged mesityl oxide. Fraction (iv) consisted mainly of the epoxide, which provided a yellow 2:4-dinitrophenylhydrazone, m. p. 126—128° undepressed on admixture with that from epoxide prepared by oxidation of mesityl oxide by alkaline hydrogen peroxide (Found: C, 48·7; H, 4·5; N, 18·1. Calc. for $C_{12}H_{14}O_5N_4$: C, 49·0; H, 4·8; N, 19·05%) (Nazarov and Akhren, *loc. cit.*, give m. p. 130—131°). Fraction (v) contained carbonyl, hydroxyl, and unsaturated groupings, and its infrared spectrum is consistent with the presence of a compound of the type 3-*hydroxy*-4-*methylpent*-4-*en*-2-*one* (IV) [Found: CO equiv., 121; active H (Zerewitinov), 0·72%. $C_6H_{10}O_2$ requires CO equiv., 114; active H, 0·88%]; it reacted with periodic acid, and also yielded a *bis*-2:4-*dinitrophenylhydrazone*, m. p. 260° (decomp.) (Found: N, 23·2. $C_{18}H_{16}O_8N_8$ requires N, 23·7%). Fraction (vi) also yielded this bis-2:4-dinitrophenylhydrazone, m. p. 260°; hydrolysis of this fraction yielded an unresolved mixture of acids and a neutral product which provided the 2:4-dinitrophenylhydrazone, m. p. 160—162° (Nazarov and Akhron, *loc. cit.*, give m. p. 156—156·5°) (Found: C, 45·8; H, 5·1. Calc. for $C_{12}H_{16}O_6N_4$: C, 46·15; H, 5·1%), of the glycol (II), identical with

that obtained by hydrolysis of the epoxide (see below). Fraction (vii), after hydrolysis, gave β-acetyl-α-methylacrylic acid (2·0 g.), m. p. and mixed m. p. 100—103° (from benzene).

From other oxidation experiments there were also isolated formaldehyde and formic acid (*p*-bromophenacyl ester).

The epoxide (fraction iv, or synthetic), heated for 2 hr. with aqueous ethanol, gave products which both provided identical 2 : 4-dinitrophenylhydrazones, m. p. 160—162°.

The epoxide concentrate (7·5 g.) was dropped slowly through a short column of activated alumina at *ca.* 250°. Distillation of the product gave a main, yellow fraction (3·0 g.), b. p. 100—120° [2 : 4-dinitrophenylhydrazone, m. p. 115—117° (from light petroleum, then aqueous alcohol) (Found : C, 49·4; H, 5·2; N, 21·0. Calc. for $C_{12}H_{14}O_5N_4$: C, 49·0; H, 4·8; N, 19·05%); dioxime, m. p. 153—155° (reported for 4-methylpentane-2 : 3-dione dioxime, m. p. 155—158°)]. Baker (*J.*, 1950, 1302) reported this diketone, b. p. 115—116° (2 : 4-dinitrophenylhydrazone, m. p. 120°).

iso*Phorone*.—*iso*Phorone (150 g.), magnesium oxide (10 g.), and cobalt naphthenate (0·1 g.) were treated with oxygen (12 l.) for 24 hr. at *ca.* 100°. The liquid-air trap contained carbon dioxide, and the carbon dioxide–alcohol trap a mixture (1 g.) of acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124—126°) and acetaldehyde (dimedone derivative, m. p. and mixed m. p. 139—140°). The main product (171·4 g.) was filtered from magnesium salts, and the filtrate, together with ether washings of the salts, distilled at 15 mm., to give fractions : (i) (3·5 g.), b. p. <85°; (ii) (108·5 g.), b. p. 85—90°; (iii) (3·8 g.), b. p. 90—110°; (iv) (0·7 g.), b. p. 110—140°; (v) (4·4 g.), b. p. 140—170°; (vi) (3·0 g.), b. p. 170—200°; residue (1·0 g.). Fraction (ii) and part of fractions (i) and (iii) were unchanged *iso*phorone, but fraction (iii) contained a compound (presumably VII) providing a *bisphenylhydrazone*, m. p. 199—200° (Found : C, 75·6; H, 7·3; N, 16·7. $C_{21}H_{26}N_4$ requires C, 75·45; H, 7·8; N, 16·8%), and a *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 276—278° (Found : C, 50·5; H, 4·2. $C_{21}H_{22}O_8N_8$ requires C, 49·0; H, 4·3%). Fractions (v) and (vi) were very viscous syrups, and analysis showed that they consisted largely of esters.

The solid magnesium salts were acidified with hydrochloric acid and extracted with ether, and the extract was distilled at 15 mm., to provide fractions : (i) (1·2 g.), b. p. 40—80°; (ii) (2·8 g.), b. p. 80—110° (mostly at *ca.* 90°); (iii) (2·3 g.), b. p. 110—140°; (iv) (6·8 g.), b. p. 140—190° (mostly at 180—190°); residue (2·8 g.). Formic and acetic acids were identified in fraction (i). Fractions (ii) and (iii) crystallised; recrystallisation from benzene gave αα-dimethylsuccinic acid, m. p. 140—141° (Found : equiv., 72·5. Calc. for $C_6H_{10}O_4$: equiv., 73). Fraction (iv) crystallised; trituration and recrystallisation from benzene gave 5 : 5-*dimethyl*-3-*oxocyclohex*-1-*enecarboxylic acid*, m. p. 153—155° (Found : C, 64·0, 64·7; H, 7·2, 7·3; active H, 0·53%; acid equiv., 169; CO equiv., 188. $C_9H_{12}O_3$ requires C, 64·3; H, 7·15; active H, 0·595%; acid and CO equiv., 168); it gave a *semicarbazone*, m. p. 224—225° (from ethanol) (Found : C, 52·3; H, 6·6. $C_{10}H_{15}O_3N_3$ requires C, 53·3; H, 6·7%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 211—212° (Found : C, 51·4; H, 4·6. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6%). After removal of the bulk of this acid, the remainder of fraction (iv) was redistilled at 15 mm., to give fractions : (iv*a*) (*ca.* 1·0 g.), b. p. <140°; (iv*b*) (0·6 g.), b. p. 140—170°; (iv*c*) (1·8 g.), b. p. 170—180°. Fractions (iv*a*) and (iv*b*) crystallised and recrystallisation from benzene–light petroleum gave ββ-dimethylglutaric anhydride, m. p. 123—125° (Found : equiv., 74·5. Calc. for $C_7H_{10}O_3$: equiv., 71). Hydrolysis provided ββ-dimethylglutaric acid, m. p. 100—101·5° (Found : equiv., 85. Calc. for $C_7H_{12}O_4$: equiv., 80). Fraction (iv*c*) provided a further quantity of the solid cyclic acid (VIII).

The acid (VIII) (0·8 g.), in methylene chloride, was treated with ozonised oxygen, the solvent removed under reduced pressure, and the ozonide decomposed by being heated for several hours with acetic acid (15 c.c.) and 30% hydrogen peroxide (10 c.c.). Ether-extraction, followed by removal of the ether and acetic acid, gave a solid residue, which after recrystallisation from benzene–light petroleum had m. p. 95—97°, undepressed on admixture with the ββ-dimethylglutaric acid obtained previously.

The author thanks Dr. D. P. Young for a sample of synthetic mesityl oxide epoxide, and the Directors of the Distillers Company Ltd. for permission to publish this paper.

Distillers Company Ltd., Dept. of Research and Development,
Great Burgh, Epsom, Surrey. [*Received, May 10th*, 1955.]

The Reactions of Potassium Hexanitrorhodate(III) *and Hexanitroiridate*(III) *with Potassium Hydrogen Difluoride.*

By R. D. Peacock.

[Reprint Order No. 6431.]

The complex fluorides K_3RhF_6 and K_3IrF_6 are formed by interaction of the corresponding tervalent complex nitrites with fused potassium hydrogen fluoride. The hydrolysis of K_3RhF_6 is described.

The preparation of fluorine compounds of the platinum metals has, with few exceptions, required the use, directly or indirectly, of elementary fluorine. Meyer and Kienitz (*Z. anorg. Chem.*, 1939, **242**, 281), however, reported making a hydrate of rhodium trifluoride from the action of concentrated hydrofluoric acid on sodium hexanitrorhodate(III) $Na_3Rh(NO_2)_6$ and stated that potassium, rubidium, and cæsium hexanitrorhodates could, under similar conditions, give the complex fluorides K_3RhF_6, Rb_3RhF_3, and Cs_3RhF_6. The reaction between potassium hexanitroiridate(III) and hydrofluoric acid has not been described.

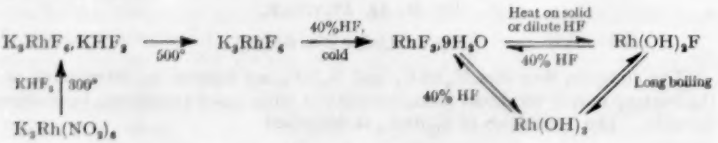
Attempts to repeat this rhodium work or to apply it to iridium have not been successful. Qualitative experiments showed that although $K_3Rh(NO_2)_6$ and $K_3Ir(NO_2)_6$ dissolve slowly in 40% aqueous hydrofluoric acid with the evolution of nitrous fumes, residues are left, even after several complete evaporations to dryness, which still contain appreciable amounts of combined nitrogen oxides. More drastic conditions are clearly required to eliminate these completely, and fusion with potassium hydrogen difluoride appeared a convenient way of attaining this end.

Potassium hexanitrorhodate(III) dissolves in potassium hydrogen difluoride, evolving nitrous fumes copiously and leaving a buff-coloured solid on cooling. According to the temperature to which the melt has been taken, two different nitrogen-free compounds are left as insoluble residues when it is leached with cold water. After being heated at about 300° the material isolated is a cubic phase of composition K_3RhF_6,KHF_2, but at about 500°, a temperature at which all the potassium hydrogen difluoride is converted into normal potassium fluoride, potassium hexafluororhodate(III) K_3RhF_6 is formed. This is a buff-coloured powder, and if prepared with dry materials has the composition represented by the formula. The variability first found in the analysis proved to be due to moisture in the starting materials. Thus a specimen of the hexafluororhodate, repeatedly fused with moist potassium hydrogen difluoride, lost potassium fluoride to such an extent that its composition approached K_2RhF_5. Potassium cryolite is said to behave in a similar manner on hydrolysis (Paine and Pearson, *J.*, 1947, 1172). The compound is almost completely insoluble in cold water, and only gradually hydrolysed by hot water, but is decomposed rapidly by moist air at 300°. It is soluble in dilute hydrochloric and sulphuric acids, evidently with hydrolysis as the complex fluoride cannot be recovered from solution.

Of special interest is the reaction with hydrofluoric acid. The salt is easily soluble in 40% hydrofluoric acid, and the solution, initially red, becomes orange in a few seconds. After evaporation nearly to dryness at room temperature, red, six-sided plates of hydrated rhodium trifluoride $RhF_3,9H_2O$ separate, which on drying at 80° form an orange-brown powder of approximate composition $Rh(OH)_2F$. The same hydroxyfluoride is obtained by either boiling or diluting the original solution in hydrofluoric acid [cf. $Al(OH)_2F$; Scott and Cowley, *J. Amer. Chem. Soc.*, 1948, **70**, 105]. $Rh(OH)_2F$ is insoluble in water, but long boiling of its suspension in water leads to the progressive loss of fluorine and eventual complete hydrolysis to the trihydroxide. With concentrated hydrofluoric acid the solution of hydrated trifluoride is re-formed.

Potassium hexanitroiridate(III) $K_3Ir(NO_2)_6$, treated with fused potassium hydrogen difluoride, yields reddish-purple potassium hexafluoroiridate(IV) K_2IrF_6, identical in properties with the material obtained by Hepworth, Robinson, and Westland (*J.*, 1954, 4268). No evidence was obtained of any complex fluorides of tervalent iridium, and it appears that under the conditions employed Ir(III) is completely oxidised to Ir(IV).

Reduction of a solution of potassium hexafluoroiridate(IV) in hydrofluoric acid with alcohol yields a green solution containing Ir(III), but attempts to isolate a pure hydrated trifluoride have not been successful.



Experimental

Potassium hexanitrorhodate, $K_2Rh(NO_2)_6$, was added in small quantities to a large excess of molten KF,HF, in which it dissolved evolving oxides of nitrogen, the colour of the melt becoming first orange and then pink as heating was continued. At about 200° the liquid became clear, and at 300° nitrogen dioxide ceased to be evolved. When cold this melt was extracted with cold water, and left a red or buff, powdery residue which was centrifuged and washed successively with cold water, alcohol, and ether, and analysed [Found: K, 37·6; Rh, 25·5; F, 36·6. Calc. for K_2RhF_6,KHF_2: K, 37·8; Rh, 25·0; F, 36·9%].

In another experiment the temperature of the melt was raised to about 500° and kept thereat until it ceased to give off hydrogen fluoride and became solid. Analysis showed the buff-coloured residue left on extraction of this material to be potassium hexafluororhodate(III) (Found: K, 35·1; Rh, 29·7; F, 34·1. Calc. for K_2RhF_6: K, 35·1; Rh, 30·8; F, 34·1%).

A solution of the hexafluororhodate in 40% hydrofluoric acid, on evaporation at laboratory temperature nearly to dryness, gave crystals of hydrated rhodium trifluoride. These were hand-picked from the solution and analysed (Found: Rh, 30·1; F, 18·4. Calc. for $RhF_3,9H_2O$: Rh, 31·9; F, 17·7%). On being heated to 80° these crystals fell to a buff-coloured powder, which analysis showed to be a hydrolytic product approaching the composition of the hydroxyfluoride [Found: Rh, 54·5; F, 12·5%; Rh : F = 1 : 1·24. Calc. for $Rh(OH)_2F$: Rh, 66·1; F, 12·2%; Rh : F = 1 : 1]. This was also formed when a solution of the hexafluororhodate in hydrofluoric acid was either diluted or heated for some time (Found: Rh, 68·2; F, 9·7%). Further washing of the hydroxyfluoride with boiling water progressively leached out the fluorine; a typical sample after being washed with 100 ml. of water had F, 2·4%.

Potassium hexanitroiridate(III) $K_2Ir(NO_2)_6$, fused with KF,HF, gave potassium hexafluoroiridate(IV) (Found: Ir, 49·5. Calc. for K_2IrF_6: Ir, 50·1%). *X*-Ray examination showed a material identical with the K_2IrF_6 described by Hepworth, Robinson, and Westland.

I am indebted to Messrs. Johnson, Matthey and Co., Ltd., for the loan of rhodium and iridium.

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NOTES.

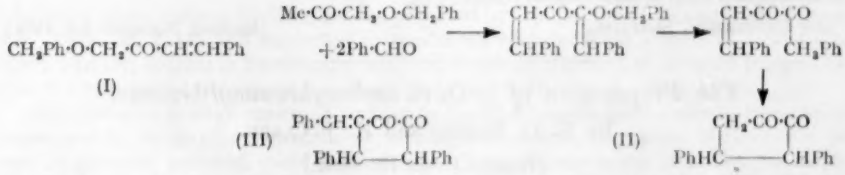
*The Action of Benzaldehyde on Benzyloxyacetone: a New cyclo*Pentane *Synthesis.*

By J. Quarterman and T. S. Stevens.

[Reprint Order No. 5844.]

Condensation between the compounds mentioned in the title was investigated as a possible route to benzyloxymethyl styryl ketone, (I). In presence of either sodium hydroxide or hydrogen chloride, the rather sluggish reaction afforded a moderate yield of a ketonic, unsaturated liquid which approximated roughly in composition to the ketone (I) and gave no iodoform reaction. The acid-catalysed process gave in addition a solid, $C_{17}H_{14}O_2$, which was identified as the 1 : 2-diphenyl*cyclo*pentane-3 : 4-dione (II) described by von Liebig (*Annalen*, **1914**, **405**, 188). The process may be formulated as shown.

The dibenzylidene derivative, as an enol ether, is hydrolysed to the unsaturated diketone, which then gives (II) by an internal Michael reaction. When more energetic acid conditions were used, the final product was the benzylidene derivative (III) of the diketone (II).



Benzyloxyacetone was not produced in tolerable yield by the Williamson synthesis or its variations, but good results were obtained by the route : $CH_2PhCl + CH_2O + KCN \longrightarrow CH_2Ph{\cdot}O{\cdot}CH_2{\cdot}CN \longrightarrow CH_2Ph{\cdot}O{\cdot}CH_2{\cdot}COMe$.

Experimental.—Benzyloxyacetonitrile. Powdered sodium cyanide (50 g.) was dissolved, with cooling, in a mixture of 40% aqueous formaldehyde (100 c.c.) and methanol (100 c.c.). After addition of benzyl chloride (110 c.c.) in methanol (200 c.c.) the mixture was heated until a gentle reaction set in, and refluxed for 5 min. thereafter. Water (250 c.c.) was added and the nitrile repeatedly extracted with ether–ligroin (b. p. 40—60°) (1 : 1). On distillation the extract gave crude nitrile, b. p. 130—170°/20 mm.; pure *benzyloxyacetonitrile* boiled at 140°/20 mm. (Found : C, 73·9; H, 6·1; N, 9·5. C_9H_9ON requires C, 73·5; H, 6·1; N, 9·5%). After concentration, the aqueous-alcoholic solution from which the nitrile had been extracted deposited a few g. of benzyloxyacetamide, long needles, m. p. 89—91° after recrystallisation from benzene–ligroin and from water (Found : N, 8·3. Calc. for $C_9H_{11}O_2N$: N, 8·5%). Darmon (*Compt. rend.*, **1933**, **197**, 1328) gives m. p. 91°.

Benzyloxyacetone. Benzyloxyacetonitrile (15 g.) was added to ethereal methylmagnesium iodide from methyl iodide (29 g.) and magnesium (5 g.). After 16 hr. the mixture was treated with dilute sulphuric acid, and the ether extract was distilled. The fraction (10 g.), b. p. 118—134° (mostly at 130°), gave the iodoform test and still contained 0·2% of nitrogen. It afforded a 2 : 4-*dinitrophenylhydrazone*, orange-yellow needles, m. p. 92—93° (Found : N, 16·2. $C_{16}H_{16}O_5N_4$ requires N, 16·2%), and a *semicarbazone*, plates, m. p. 113—114° (Found : C, 60·0; H, 6·5; N, 19·4. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·5; N, 19·0%); the slightly impure ketone was used in subsequent experiments. No benzyloxyacetone could be obtained from chloroacetone and sodium benzyl oxide. When chloroacetone (1 g.) and benzyl alcohol (1 g.) were heated for 3 hr. at 100° in presence of (*a*) pyridine (1 g.), (*b*) calcium carbonate (1 g.), (*c*) barium hydroxide (1 g.), or (*d*) calcium hydroxide (1 g.), the yield of benzyloxyacetone was respectively 21, 3, 35, and 14%, as determined in the fraction, b. p. 120—130°/20 mm., of neutral material by Vandoni and Desseigne's hydroxylamine method (*Bull. Soc. chim. France*, **1935**, **11**, 1685). These materials gave the dinitrophenylhydrazone described above.

Condensation with benzaldehyde. (*a*) Benzyloxyacetone (15 c.c.) and benzaldehyde (7 c.c.) were heated with 25% aqueous sodium hydroxide (2 c.c.) and enough dioxan to form a homogeneous solution, for 72 hr. at 100°. The product, dissolved in ether, washed, and distilled, gave a yellow oil (5 g.), b. p. 205—215°/14 mm. (mostly 210—212°). (*b*) Dry hydrogen chloride was passed for 5 min. into a mixture of benzyloxyacetone (6 g.) and benzaldehyde (2·3 g.). After 24 hr. the mixture was dissolved in ether, washed with sodium hydrogen carbonate solution, and distilled. The resulting yellow oil, b. p. 210—220°/20 mm., deposited yellow crystals which were washed with ligroin. The remaining oil, repeatedly distilled, boiled at 205—208°/12 mm. [Found : C, 78·5; H, 6·6%; *M* (Rast), 225. Calc. for $C_{17}H_{16}O_2$: C, 80·9; H, 6·3%; *M*, 252]. The yellow solid crystallised from ethanol (charcoal) in colourless needles, saturated to bromine and permanganate (Found : C, 81·5; H, 5·6. Calc. for $C_{17}H_{14}O_2$: C, 81·6; H, 5·6%). The m. p., 176—177°, was not depressed on admixture with diphenyl*cyclo*pentanedione prepared by von Liebig's method; the two preparations also afforded identical diacetyl derivatives, m. p. and mixed m. p. 145°. (*c*) A stream of dry hydrogen chloride was passed for 3 hr. through a mixture of benzyloxyacetone (14 g.) and benzaldehyde (8 g.), and the whole kept at room temp. for 48 hr. When shaken with ether and sodium hydrogen carbonate solution it deposited a yellow powder (9 g.) which crystallised from acetic acid in needles, m. p. 219—221°, very sparingly soluble in ethanol (Found : C, 84·5; H, 5·4. Calc. for $C_{34}H_{28}O_3$: C, 85·2; H,

5·3%). von Liebig reports that benzylidenediphenyl*cyclo*pentanedione melts at 223° and is difficult to burn quantitatively.

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THE UNIVERSITY, SHEFFIELD. [*Received, November 3rd*, 1954.]

The Preparation of p-*Di*-(6-*carboxyhexanoyl*)*benzene.*

By G. D. PARKES and K. J. CLARK.

[Reprint Order No. 6082.]

THE sodium derivative of tri(tetrahydro-2-pyranyl) pentane-1 : 1 : 5-tricarboxylate reacts with terephthaloyl dichloride in benzene. Decomposition of the product with acetic acid gives a small yield of *p*-di-(6-carboxyhexanoyl)benzene. Attempts to prepare *p*-di-(4-carboxybutanoyl)benzene by a similar method, using propane-1 : 1 : 3-tricarboxylic acid, were unsuccessful. The use of the benzyl ester method was unsuccessful for both acids (cf. Bowman, *J.*, 1950, 325; Bowman and Fordham, *Chem. and Ind.*, 1951, 742; *J.*, 1952, 3945). These experiments are the preliminary to an attempt to synthesise interlocking carbon rings.

Experimental.—Ethyl δ-bromovalerate was prepared from ethyl hydrogen adipate by the procedure recorded for the methyl ester (*Org. Synth.*, 1946, **26**, 52; Archer and Pratt, *J. Amer. Chem. Soc.*, 1944, **66**, 1656; Hunsdiecker, *Ber.*, 1942, **75**, 291; Merchant *et al.*, *J. Amer. Chem. Soc.*, 1927, **49**, 1828). The yield of ester, b. p. 120°/15 mm., 129°/35 mm., was 51%.

Triethyl pentane-1 : 1 : 5-tricarboxylate was prepared by the interaction of δ-bromovaleric ester and sodiomalonic ester according to the method of Cheney and Piening (*J. Amer. Chem. Soc.*, 1945, **67**, 931) who used δ-chlorovaleric ester. The yield of ester, b. p. 177—184°/13—15 mm., was 69%. Pentane-1 : 1 : 5-tricarboxylic acid was then obtained by their method (*loc. cit.*).

p-*Di*-(6-*carboxyhexanoyl*)*benzene* (cf. Bowman and Fordham, *loc. cit.*). Pentane-1 : 1 : 5-tricarboxylic acid (10·2 g., 0·05 mole) was added in small portions to a solution of redistilled dihydropyran (18 g., 0·225 mole) in "AnalaR," sodium-dried benzene (50 ml.) containing 1 drop of concentrated sulphuric acid at <30°, with exclusion of moisture. After one day, the resulting clear solution was freed from traces of free acid by shaking it with solid potassium hydroxide (4 g.) for 0·5 hr., the solution was decanted, and the solvent and excess of dihydropyran were removed by distillation under reduced pressure at <30°.

The residual ester in benzene (50 ml.) was added to sodium powder (1·15 g.) in benzene (100 ml.) at <35°. When the sodium had dissolved, terephthaloyl chloride (4·9 g., 0·02 mole) in benzene (50 ml.) was added. After storage with occasional shaking for 1 hr. and stirring for a further 1½ hr., acetic acid (6 ml.) was added and the mixture boiled until evolution of carbon dioxide ceased. The cooled mixture was washed with water. A white solid, insoluble in both layers, was precipitated: when recrystallised from water this had m. p. 185—195°. The aqueous layer, saturated with salt and extracted with ether, yielded nothing. The benzene layer, when dried overnight over sodium sulphate, deposited thereon a solid, which was separated by dissolving the whole solid in boiling water and cooling: this product had m. p. 185—195°. The benzene was removed under pressure, an oil (b. p. 90—95°/30 mm., 6·85 g.) distilling; the residual yellow solid did not crystallise from alcohol or acetic acid but separated therefrom as an amorphous powder, m. p. 205—230°; analysis indicated that it was a mixture of mono- and di-acids (Found: C, 64·9; H, 6·8. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1. Calc. for $C_{20}H_{26}O_6$: C, 66·3; H, 7·2%). Separation was achieved by fractional extraction with boiling water (21 × 200 ml.). Material separating from the last eleven fractions was combined and appeared to consist of p-*di*-(6-*carboxyhexanoyl*)*benzene* (Found: C, 65·87; H, 7·1. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%), though no determination of equivalent weight was made.

Propane-1 : 1 : 3-tricarboxylic ester was obtained according to the directions of Ruzicka *et al.* (*Helv. Chim. Acta*, 1934, **17**, 183) and converted into the acid by Cheney's method (*loc. cit.*).

The authors thank Sir Robert Robinson for his interest and advice.

DYSON PERRINS LABORATORY, OXFORD. [*Received January 28th*, 1955.]

The Synthesis and Cleavage of 9-Phenanthryl Phenyl Ether.

R. L. Huang.

[Reprint Order No. 6157.]

9-Phenanthryl phenyl ether has been prepared by the method of Ullmann and Sponagel (*Ber.*, 1905, **38**, 2212) and subjected to treatment with reagents known to cleave diaryl ethers, namely, sodium in liquid ammonia, and Grignard reagents at elevated temperatures or in the presence of anhydrous cobaltous chloride (cf. Huang, *J.*, 1954, 3084).

Reaction with a large excess of sodium in liquid ammonia gave quantitative yields of phenol and 9 : 10-dihydrophenanthrene, although when only two atoms of the metal were used no phenolic material could be isolated. Since phenanthrene is known to undergo reduction under the same conditions (Hückel and Bretschneider, *Annalen*, 1939, **540**, 183), these results strongly suggest that in the case of the phenanthryl ether the reaction which first took place exclusively was reduction of the phenanthrene nucleus at the 9 : 10-position, the reduced ether then suffering cleavage to phenol with excess of sodium, as would a substituted benzyl ether.

Heating the ether with methylmagnesium iodide at 200° resulted in a complex mixture from which were obtained phenol (corresponding to a 4% cleavage), unchanged ether (51%), and intractable oils. Cleavage by *n*-butylmagnesium bromide and cobaltous chloride in the manner previously described (Huang, *loc. cit.*) occurred only to a small extent (10%), yielding a mixture of phenol and 9-phenanthrol in a molar ratio of 76 : 24. It is not certain whether reduction of the phenanthrene nucleus occurred before cleavage; if it had, it could not have been extensive, since an attempt to isolate 9 : 10-dihydrophenanthrene by chromatography was unsuccessful. (Phenanthrene itself was found to be unaffected by this treatment.) The relatively high proportion of phenol seems to be a common feature with two other polynuclear aryl ethers so far studied, namely, α- and β-naphthyl phenyl ether, the former giving on cleavage 69 mole % of phenol (Kharasch and Huang, *J. Org. Chem.*, 1952, **17**, 669) and the latter, 65 mole % (Huang, unpublished result).

Experimental.—*9-Phenanthryl phenyl ether.* 9-Bromophenanthrene (35 g.) was heated with a mixture of potassium hydroxide (10 g.) and phenol (31 g.) for 2 hr. at 250° (reaction being incomplete at 200° after 4 hr.). The *ether* was isolated by extraction with benzene and distilled (b. p. 201—210/1 mm.). It crystallised from benzene–ethanol in prisms, m. p. 80—81° (17 g.), and exhibited a violet fluorescence in solution (Found: C, 89·2; H, 5·3. $C_{20}H_{14}O$ requires C, 88·9; H, 5·2%).

Cleavage experiments. (*a*) 9-Phenanthryl phenyl ether (10·8 g.) in diethyl ether (75 c.c.) was added to a solution of methylmagnesium iodide (from 43 g. of methyl iodide and 7·7 g. of magnesium) in ether (150 c.c.). The solvent was distilled off and the mixture heated at 200° for 7 hr. After cooling, moist ether was added, followed by water and dilute sulphuric acid. The product was taken into ether and the phenolic fraction extracted with aqueous potassium hydroxide (10%, followed by 20%). This extract on acidification gave phenol (0·15 g.) which was steam-distilled, titrated iodometrically, and identified in the usual way. The neutral fraction was chromatographed on alumina, giving the starting material (5·5 g.) and small fractions of brown oils.

(*b*) 9-Phenanthryl phenyl ether (8·1 g.) was treated with *n*-butylmagnesium bromide (from 21 g. of *n*-butyl bromide and 3·6 g. of magnesium) and anhydrous cobaltous chloride (11 g.) in the usual way. From the product an alkali-soluble fraction was obtained which on steam-distillation gave, in the distillate, phenol (0·21 g.) and, in the residue, 9-phenanthrol (0·14 g.), m. p. 155—156° after recrystallisation from benzene–*cyclo*hexane (lit., m. p. 158°). The neutral fraction, on treatment with ethanol, deposited the unchanged phenanthryl ether (4·1 g.) which was filtered off. The filtrate was concentrated and adsorbed on alumina. Elution with benzene followed by benzene–acetone (20 : 1) gave more phenanthryl ether (*ca.* 1 g.) and small fractions of brown oils.

(*c*) 9-Phenanthryl phenyl ether (2·0 g.) in diethyl ether (*ca.* 20 c.c.) was added to liquid ammonia (*ca.* 200 c.c.). With vigorous stirring, sodium (2·5 g., 8 atoms per mole of ether) was added in small pieces during 1 hr., and after a further 2 hours' stirring powdered ammonium chloride was introduced. After evaporation of the ammonia followed by addition of water

(25 c.c.), the product was taken up in ether, and the phenolic fraction isolated by alkali-extraction and estimated in the usual manner, giving phenol (0·6 g.) but no phenanthrol. The neutral fraction was dissolved in light petroleum–benzene (1 : 1) and passed through a column of alumina, then distilled, giving 9 : 10-dihydrophenanthrene (1·3 g.) b. p. 92—97° (bath)/0·5 mm., n_D^{24} 1·6397 [Durland and Adkins report n_D^{25} 1·6406 (*J. Amer. Chem. Soc.*, **1937**, **59**, 135)] (Found : C, 93·15, 93·0; H, 6·8, 6·8. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%). A similar reduction with only 2 atoms of sodium per mole of the ether gave no phenolic material.

The author thanks Sir Robert Robinson, O.M., F.R.S., for laboratory facilities.

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*Synthesis of β-Amino-sulphones and αβ-Unsaturated Sulphones. Part II.**

By M. BALASUBRAMANIAN, V. BALIAH, and T. RANGARAJAN.

[Reprint Order No. 6234.]

IN Part I *, the preparation of β-amino-sulphones and αβ-unsaturated sulphones by use of arylsulphonylacetic acids was described. The present communication deals with the preparation of similar compounds with alkylsulphonylacetic acids. The condensation of these acids with salicylaldehyde yielded 3-alkylsulphonylcoumarins (cf. Tröger and Bolte, *J. prakt. Chem.*, **1921**, **103**, **163**; Tröger and Dunkel, *ibid.*, **1922**, **104**, 311).

Experimental.—Alkylsulphonylacetic acids. The alkylthioacetic acids (Larsson, *Ber.*, **1930**, **63**, 1347) were oxidised in acetone at room temperature by the addition of an excess of a 5%

TABLE 1. *β-Amino-sulphone hydrochlorides*, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CHR'{\cdot}NH_2,HCl$.

No.	R'	Yield (%) *	M. p.	Formula	Found (%) C	H	Cl^-	Required (%) C	H	Cl^-
				R = Me						
1	Ph	(6) ª								
2	3 : 4-$(CH_2O_2)C_6H_3$	11(10)	248—250° (d)	$C_{10}H_{13}O_4NS,HCl$	—	—	12·5	—	—	12·7
3	*o*-C_6H_4Cl	20(3)	195—197	$C_9H_{10}O_2NClS,HCl$	—	—	13·1	—	—	13·1
4	*m*-$NO_2{\cdot}C_6H_4$	14(16)	202—203	$C_9H_{12}O_4N_2S,HCl$	38·5	4·8	12·6	38·5	4·6	12·6
				R = Et						
5	Ph	(6) ª								
6	3 : 4-$(CH_2O_2)C_6H_3$	20(5)	206—208 (d)	$C_{11}H_{15}O_4NS,HCl$	44·9	5·55	12·4	45·0	5·45	12·1
7	*o*-C_6H_4Cl	21 ᵇ	209—210	$C_{10}H_{12}O_2NClS,HCl$	—	—	12·1	—	—	12·5
8	*o*-$NO_2{\cdot}C_6H_4$	18(4)	220—222 (d)	$C_{10}H_{14}O_4N_2S,HCl$	41·2	5·0	11·9	40·9	5·1	12·1
9	*m*-$NO_2{\cdot}C_6H_4$	20(17)	146—148	$C_{10}H_{14}O_4N_2S,HCl$	—	—	12·1	—	—	12·1
10	*o*-$OH{\cdot}C_6H_4$	14 ᶜ	211—213 (d)	$C_{10}H_{13}O_3NS,HCl$	45·2	6·05	13·0	45·2	6·0	13·4
				R = Pr						
11	*o*-C_6H_4Cl	23(6)	208—210	$C_{11}H_{14}O_2NClS,HCl$	—	—	11·8	—	—	11·9
12	*m*-$NO_2{\cdot}C_6H_4$	30 ᵇ	144—146	$C_{11}H_{16}O_4N_2S,HCl,H_2O$	40·7	5·8	10·7	40·4	5·8	10·9
				R = Bu						
13	3 : 4-$(CH_2O_2)C_6H_3$	7 ᵇ	164—166	$C_{12}H_{19}O_4NS,HCl$	48·6	6·3	11·1	48·5	6·2	11·0
14	*o*-C_6H_4Cl	11 ᵇ	192—194	$C_{12}H_{18}O_2NClS,HCl,H_2O$	43·5	6·5	11·1	43·6	6·4	10·8
15	*m*-$NO_2{\cdot}C_6H_4$	12 ᵇ	182—184	$C_{12}H_{18}O_4N_2S,HCl$	44·5	5·9	10·8	44·65	5·9	11·0
				R = $PhCH_2$						
16	Ph	18(18)	223—224	$C_{15}H_{17}O_3NS,HCl$	—	—	11·6	—	—	11·4
17	3 : 4-$(CH_2O_2)C_6H_3$	(7) ª	—	—	—	—	—	—	—	—
18	*o*-C_6H_4Cl	21(10)	226—228	$C_{15}H_{16}O_2NClS,HCl$	—	—	10·3	—	—	10·3
19	*p*-C_6H_4Cl	20(14)	228—230	$C_{15}H_{16}O_2NClS,HCl$	—	—	10·4	—	—	10·3
20	*m*-$NO_2{\cdot}C_6H_4$	22(20)	277—279 (d)	$C_{15}H_{16}O_4N_2S,HCl$	50·4	4·9	9·4	50·5	4·8	9·95
21	*o*-$OH{\cdot}C_6H_4$	7 ᶜ	225—227 (d)	$C_{15}H_{17}O_3NS,HCl$	—	—	11·1	—	—	10·8

* The percentage yields in the parentheses are those of the αβ-unsaturated sulphones.
ª No β-amino-sulphone could be isolated. ᵇ No unsaturated sulphone could be isolated. ᶜ Coumarins formed are described in Table 4. (d) M. p. with decomp.

* *J.*, 1954, 1844, is now regarded as Part I.

solution of potassium permanganate. The excess of permanganate was then removed with sulphur dioxide, and the solution evaporated to dryness under reduced pressure. The residue was extracted with acetone and dried ($MgSO_4$), and the solvent removed. Ethyl-, propyl-, and butyl-sulphonylacetic acids solidified only after being kept in a vacuum-desiccator. Benzylsulphonylacetic acid was obtained by oxidising the alkylthio-acid in acetic acid with hydrogen peroxide (30%), concentrating the solution, and extracting it with boiling benzene. *Propylsulphonylacetic acid* melted at 41° (Found: C, 36·4; H, 6·0. $C_5H_{10}O_4S$ requires C, 36·15; H, 6·0%). It was hygroscopic. The other sulphonylacetic acids had m. p.s given in the literature (methyl: Mellander, *Svensk Kem. Tidskr.*, 1934, **46**, 99. Ethyl and benzyl: Rothstein, *J.*, 1937, 309. Butyl: Pomerantz and Connor, *J. Amer. Chem. Soc.*, 1939, **61**, 3139).

Condensation of alkylsulphonylacetic acids with aldehydes and ammonia. The condensation was effected as described for arylsulphonylacetic acids in Part I. The data relating to the β-amino-sulphone hydrochlorides, the bases, and the αβ-unsaturated sulphones are recorded in Tables 1—3 respectively.

2-Benzylamino-2-phenylethyl methyl sulphone hydrochloride. A mixture of methylsulphonylacetic acid (1·38 g.), benzaldehyde (1·06 g.), and benzylamine (1·07 g.) in acetic acid (2 c.c.) was

TABLE 2. *β-Amino-sulphones*, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CHR'{\cdot}NH_2$ (*free bases*; *the nos. refer to the corresponding compounds in Table* 1).*

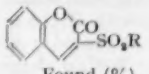
No.	M. p.	Found (%) C	Found (%) H	Required (%) C	Required (%) H	Formula
2	146—147°	49·25	5·45	49·4	5·35	$C_{10}H_{13}O_4NS$
3	77—79	43·1	5·8	42·9	5·6	$C_9H_{13}O_3NClS,H_2O$
7	72—73	45·3	5·9	45·2	6·0	$C_{10}H_{14}O_3NClS,H_2O$
9	101—102	46·6	5·6	46·5	5·4	$C_{10}H_{14}O_4N_2S$
11	44—45	50·7	6·5	50·5	6·1	$C_{11}H_{16}O_2NClS$
16	88—89	65·4	6·0	65·5	6·0	$C_{18}H_{17}O_2NS$
18	100—102	54·9	5·6	55·0	5·5	$C_{12}H_{16}O_3NClS,H_2O$
19	127—128	58·0	5·1	58·2	5·2	$C_{15}H_{16}O_2NClS$
21	153—154	61·9	5·4	61·9	5·8	$C_{18}H_{17}O_2NS$

* Prepared from the hydrochlorides by means of aqueous ammonia and recrystallised from water or aqueous ethanol.

TABLE 3. *αβ-Unsaturated sulphones*, $R{\cdot}SO_2{\cdot}CH{:}CHR'$.

R	R′	M. p.	Solvent	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Me	3 : 4-$(CH_2O_2)C_6H_3$	129—130°	MeOH	$C_{10}H_{10}O_4S$	52·7	4·2	53·1	4·4
Me	*o*-C_6H_4Cl	82—83	,,	$C_9H_9O_4ClS,H_2O$ *	46·4	4·5	46·15	4·7
Me	*m*-$NO_2{\cdot}C_6H_4$	130—132	,,	$C_9H_9O_4NS$	47·7	3·7	47·6	3·9
Et	Ph	66—67	H_2O	$C_{10}H_{12}O_3S,H_2O$ *	56·5	6·4	56·1	6·5
Et	3 : 4-$(CH_2O_2)C_6H_3$	80—81	,,	$C_{11}H_{12}O_4S$	55·3	4·9	55·0	5·0
Et	*o*-$NO_2{\cdot}C_6H_4$	89—90	,,	$C_{10}H_{11}O_4NS$	50·2	4·5	49·8	4·6
Et	*m*-$NO_2{\cdot}C_6H_4$	124—125	EtOH	$C_{10}H_{11}O_4NS$	50·1	4·5	49·8	4·6
Pr^n	*o*-C_6H_4Cl	76—77	MeOH	$C_{11}H_{12}O_3ClS,H_2O$ *	50·2	5·8	50·3	5·7
$PhCH_2$	Ph	144—145	CCl_4	$C_{15}H_{14}O_2S$	69·85	5·05	69·8	5·4
$PhCH_2$	3 : 4-$(CH_2O_2)C_6H_3$	150—151	EtOH	$C_{16}H_{14}O_4S$	63·6	4·7	63·6	4·6
$PhCH_2$	*o*-C_6H_4Cl	111—112	MeOH	$C_{15}H_{13}O_3ClS,H_2O$ *	58·2	4·7	58·0	4·8
$PhCH_2$	*p*-C_6H_4Cl	163—165	CCl_4	$C_{15}H_{13}O_2ClS,H_2O$ *	57·55	4·5	58·0	4·8
$PhCH_2$	*m*-$NO_2{\cdot}C_6H_4$	184—186	EtOH	$C_{15}H_{13}O_4NS$	59·4	4·3	59·4	4·3

* Since their analyses indicated water of crystallisation (which could not be removed by drying *in vacuo*) the possibility of these compounds' having the β-hydroxy-sulphone structure, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CH(OH){\cdot}R'$, was considered. However, the compounds decolorised bromine in carbon tetrachloride and were recovered unchanged as hydrates after attempted acetylation or benzoylation. They also readily decolorised potassium permanganate in aqueous acetone.

TABLE 4. *3-Alkylsulphonylcoumarins*, 

R	Yield (%)	M. p.*	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Me	6	184—185°	$C_{10}H_8O_4S$	53·1	3·9	53·6	3·6
Et	14	163—164	$C_{11}H_{10}O_4S$	55·1	4·3	55·5	4·2
Pr^n	12	140—141	$C_{12}H_{12}O_4S$	57·0	4·7	57·15	4·8
Bu^n	12	122—123	$C_{13}H_{14}O_4S$	58·35	5·4	58·6	5·3
CH_2Ph	20	161—162	$C_{16}H_{12}O_4S$	64·1	3·8	64·0	4·0

* Crystallised as needles from methanol.

refluxed for 10 min., cooled, and extracted with ether, and the extract was saturated with hydrogen chloride. The precipitated *hydrochloride* (0·3 g.), when crystallised from ethanol–ether, had m. p. 179—181° (Found: C, 55·7; H, 6·4; Cl^-, 10·5. $C_{16}H_{19}O_3NS,HCl,H_2O$ requires C, 55·9; H, 6·4; Cl^-, 10·3%). The filtrate obtained after removal of the above hydrochloride, yielded methyl ω-styryl sulphone (0·6 g.), m. p. 79—80° (from water). Truce, Simms, and Hill (*J. Amer. Chem. Soc.*, **1953**, **75**, 5411) record m. p. 78—79°.

Benzyl 2-benzylamino-2-phenylethyl sulphone. By use of benzylsulphonylacetic acid (2·14 g.), benzaldehyde (1·06 g.), and benzylamine (1·07 g.) in acetic acid (2 c.c.), the condensation was effected as above. Addition of ether precipitated benzyl ω-styryl sulphone (0·6 g., see Table 3) which was filtered off, and from the filtrate the *hydrochloride* (0·35 g.) was obtained, having m. p. 187—189° (from ethanol–ether) (Found: Cl^-, 9·0. $C_{22}H_{23}O_2NS,HCl$ requires Cl^-, 8·8%). The *base* was obtained by treatment of the hydrochloride with aqueous ammonia, m. p. 108—109° (from ethanol–water) (Found: C, 69·2; H, 6·5. $C_{22}H_{23}O_2NS,H_2O$ requires C, 68·9; H, 6·5%).

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Chemistry of the Coprosma *Genus. Part X.* The Colouring Matters from* Coprosma rhamnoides.

By Lindsay H. Briggs and A. R. Taylor.

[Reprint Order No. 6253.]

Coprosma rhamnoides (Oliver, "The Genus *Coprosma*," Bernice P. Bishop Museum Bull. 132, 1935) is a small shrub, 2—6 feet high, occurring throughout New Zealand to which it is endemic. As already reported (Part VIII, *J.*, 1954, 3940) the stem-bark contains asperuloside but no appreciable amount of colouring matter. The root-bark, however, is bright yellow.

Concentration of aqueous extracts of the root-bark afforded rutin. Chromatography of an acetone extract on magnesia gave a series of coloured bands from which rutin, anthragallol 1 : 2-dimethyl ether, and rubiadin 1-methyl ether were isolated.

Complete chromatography, based on a 1 : 1 mixture of magnesium carbonate and diatomaceous earth, gave more than three bands. Several of the lower bands, however, all gave the same product, rubiadin 1-methyl ether, and the material from single bands also gave two bands on rechromatography, from both of which, however, again only rubiadin 1-methyl ether was isolated.

It has been previously observed that other pure compounds in this series, such as 1-hydroxyanthraquinone, gave two bands on chromatography, from both of which the pure compound can be regenerated. Chromatography of hydroxyanthraquinones on magnesium oxide or carbonate columns is a phenomenon not necessarily of simple physical absorption with no colour change but mainly of chemical combination similar to ion-exchange, leading to differently coloured magnesium salts. The double bands in this case may be due to the two different types of absorption.

Experimental.—The analyses are by Dr. T. S. Ma, University of Otago.

The root-bark of *Coprosma rhamnoides* was collected in January from specimens growing at Piha. The ground, air-dried bark was first extracted with light petroleum (b. p. 50—65°) to remove wax and then with boiling water in a Soxhlet apparatus for 40 hr. Concentration of the extract to one-hundredth of the original volume afforded a single component (yield, *ca.* 10%), identified as rutin. Repeated crystallisation from water yielded minute, yellow needles, m. p. *ca.* 186°, decomp. above 200°, undepressed by authentic rutin. After drying at 100° the material was extremely hygroscopic (Found: C, 53·6, 53·35; H, 5·5, 5·5. Calc. for $C_{27}H_{30}O_{16}$: C, 53·4; H, 4·9%).

The glycoside was hydrolysed with 2% sulphuric acid solution at 100° for 7 hr. The insoluble aglycone crystallised from 60% acetic acid in rods, m. p. and mixed m. p. with quercetin, 316—316·5° (Found: C, 59·65; H, 3·8. Calc. for $C_{15}H_{10}O_7$: C, 59·6; H, 3·3%). The derived

* Part IX, *J.*, 1954, 4182.

acetate had m. p. 191—192° (lit., m. p. 193·5°) and the pentamethyl ether m. p. 157—157·5° (lit., m. p. 151—152°).

The aqueous solution from the hydrolysis was neutralised on an ion-exchange column (Amberlite IRA-404) and concentrated to a small volume, and an aliquot part was treated in the usual way with phenylhydrazine. Microscopical examination of the osazones formed showed the presence of two types of crystal, long thin rods and curved needles, characteristic of glucosazone and rhamnosazone respectively (Hassid and McReady, *Ind. Eng. Chem. Anal.*, 1942, **14**, 883). Paper chromatography of a drop of the solution, with butanol–pyridine–water (Hough, Jones, and Wadman, *J.*, 1950, 1702) for 28 hr., and aniline hydrogen phthalate as spray, afforded two spots, identified with glucose and rhamnose from control experiments.

Chromatographic separation. The bark from the aqueous extraction was dried and extracted to completion with acetone. Rubiadin 1-methyl ether separated from the extract on cooling. Separation was best achieved by chromatography on a 1 : 1 mixture of magnesium carbonate and diatomaceous earth which gave even bands throughout. The material recovered from the bands by treatment with dilute hydrochloric acid was then rechromatographed on smaller columns.

The top band afforded rutin, m. p. and mixed m. p. 186°, after crystallisation from water. The material from the second major, dark orange band crystallised from alcohol in rhombohedral plates, m. p. and mixed m. p. with anthragallol 1 : 2-dimethyl ether, 238°. The colour reactions also agreed with this identification.

The lower bands varied in colour through yellow to brown and exhibited tailing with pinkish tints. Rechromatography of apparently single bands also afforded bands of similar colour with marked tailing. Isolation of the anthraquinone compounds from these bands, however, failed to yield any compound other than rubiadin 1-methyl ether, which was obtained as yellow needles, m. p. and mixed m. p. 290°, after crystallisation from glacial acetic acid (Found: C, 71·1; H, 4·8. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%). The colour reactions, the acetate, m. p. and mixed m. p. 175—176°, and the fully methylated ether, m. p. and mixed m. p. 159—161° (cf. Part I, *J.*, 1948, 564), confirmed the identification.

We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science and the Research Grants Committee of the University of New Zealand for grants, to Messrs. Rohm and Haas Company, Philadelphia, for the gift of chemicals, and to Mr. D. E. Cooper, M.Sc., for practical assistance.

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N′-2 : 4-*Dinitrophenyl*-NN-*phthaloylhydrazine.*

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[Reprint Order No. 6268.]

2 : 4-Dinitrophenylhydrazine was reported by Cerezo and Olay (*Anales Fis. Quim.*, 1934, **32**, 1090) to condense with dibasic acids, *e.g.*, succinic or phthalic acid, to give *NN*- or *NN′*-derivatives, $X<[CO]_2>N{\cdot}NHAr$ or $X\begin{smallmatrix}CO{\cdot}NH\\ \\ CO{\cdot}NAr\end{smallmatrix}$. This reaction with phthalic acid is rapidly effected in boiling dioxan in presence of phosphoric oxide or zinc chloride, the yield being 50%.

With nitrous oxides in acetic acid (Hötte, *J. prakt. Chem.*, 1887, **35**, 265) or with fuming nitric acid in acetic–sulphuric acid *N′*-phenyl-*NN*-phthaloylhydrazine gives a dinitro-derivative; Hötte (*loc. cit.*) located one nitro-group on nitrogen, and Ohta (*J. Pharm. Soc. Japan*, 1944, **64**, No. 10A, 49) placed the other as in a *p*-nitrophenyl group. The product is, however, identical (mixed m .p.) with *N′*-2 : 4-dinitrophenyl-*NN*-phthaloylhydrazine prepared as above.

Condensation as above gives *ca.* 55% yields of various imides and hydrazides. We have thus prepared: *N*-phenyl-, *N*-*p*-nitrophenyl-, *N*-*p*-tolyl-, and *N*-1-naphthyl-succinimide; *N′*-phenyl- and *N′*-2 : 4-dinitrophenyl-*NN*-succinylhydrazine; and the corresponding phthaloyl derivatives. Acetanilide, benzanilide, and benzo-*m*-toluidide were similarly prepared.

Experimental.—Preparation of N'-phenyl-NN-phthaloylhydrazine. Phthalic acid (1·66 g., 0·01 mole), phenylhydrazine (1·08 g., 0·01 mole), and anhydrous zinc chloride (3 g.) in dioxan (20 ml.) were refluxed for 2 hr., then allowed to cool and poured on crushed ice. A yellow solid separated which was filtered off and recrystallised either from hot ethyl alcohol and a few drops of water, or from acetone, giving uniform yellow prisms, m. p. 184° (55%).

Nitration of N'-phenyl-NN-phthaloylhydrazine. The hydrazide (0·8 g.) was dissolved in hot glacial acetic acid (6 ml.). To the cold solution concentrated sulphuric acid (2 ml.) was added drop by drop with shaking, then similarly nitric acid (*d* 1·45; 2 ml.). After 10 min. the mixture was poured on crushed ice. The yellowish-orange product was filtered off and recrystallised from aqueous alcohol or glacial acetic acid (charcoal), giving yellow crystals, m. p. 270—272° (decomp.) (0·58 g.).

Preparation of N'-2 : 4-dinitrophenyl-NN-phthaloylhydrazine. Phthalic acid (1·66 g., 0·01 mole), 2 : 4-dinitrophenylhydrazine (1·98 g., 0·01 mole), and anhydrous zinc chloride (3 g.) in dioxan (20 ml.) were refluxed for 2 hr., allowed to cool, and poured on crushed ice. The solid product was filtered off and recrystallised from boiling glacial acetic acid (charcoal). Yellow crystals (50%) were obtained, having m. p. 272—274° (decomp.) alone or mixed with the preceding product.

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The Electrical Conductivity of Sulphuric Acid.

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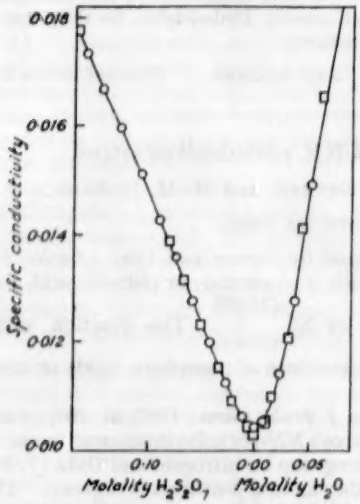
[Reprint Order No. 6285.]

BEFORE making measurements of the electrical conductivity of solutions in sulphuric acid (Hetherington, Nichols, and Robinson, *J.*, in the press), it was desirable to repeat those made on the system water–sulphur trioxide in the equimolecular region: first, because the



Some specific conductivities of the water–sulphur trioxide system.

○ Present authors.
□ Gillespie and Wasif.

specific conductivities reported within the last 25 years differ by 0·00027 ohm^{-1} cm.$^{-1}$; secondly, because the determinations provide a convenient check on the technique we intended to use; and, lastly, because the measurement of conductivity furnishes the most convenient and accurate means of characterising our solvent. This note simply deals with the preparation of the solutions and presents the results which, when considered in relation to the published figures, are thought to narrow the limits within which the conductivity of

sulphuric acid lies. The cell used and the method of measurement will be described in a later communication.

Since Kohlrausch (*Wied. Ann.*, 1882, **17**, 69) and Knietsch (*Ber.*, 1901, **34**, 4107) sought to establish the composition corresponding to minimum conductivity in the system H_2O–SO_3—recently shown by Kunzler and Giauque (*J. Amer. Chem. Soc.*, 1952, **74**, 804) to be 99·996 ± 0·001% (by wt.) sulphuric acid at 10·37°—six determinations of the specific conductivity of sulphuric acid at 25° have appeared, as follows :

	ohm^{-1} cm.$^{-1}$
(i) Hantzsch (*Z. physikal. Chem.*, 1907, **61**, 257)	0·0098
(ii) Lichty (*J. Amer. Chem. Soc.*, 1908, **30**, 1834)	0·01041
(iii) Bergius (*Z. physikal. Chem.*, 1910, **72**, 338)	0·0097
(iv) Ussanowitsch, Sumarakowa, and Udowenko (*Acta Phys. Chim. U.R.S.S.*, 1939, **11**, 505)	0·0106
(v) Reinhardt (*J. Amer. Chem. Soc.*, 1950, **72**, 3359)	0·0108
(vi) Gillespie and Wasif (*J.*, 1953, 204)	0·01033

To these we add a seventh, *viz.*, 0·01045 ohm^{-1} cm.$^{-1}$.

Our value is almost identical with (ii) and only 0·00012 ohm^{-1} cm.$^{-1}$ above the last determination (vi). A large-scale plot of conductivities against composition, over the range 0·2 mole H_2O to 0·4 mole $H_2S_2O_7$ which we covered, shows that our points lie very close to those of Gillespie and Wasif (*loc. cit.*), except at the minimum value, where they are a little higher. These authors have given reasons for doubting the accuracy of determinations (i), (iv), and (v) that seem well founded, and (iii) is very low. Thus we are left with determinations (ii), (vi), and our own which, from their concordance, suggest that the mean, 0·01040 ohm^{-1} cm.$^{-1}$, is very close to the conductivity of absolute sulphuric acid at 25°.

Experimental.—The starting materials were dilute oleum and water. The former was prepared by passing sulphur trioxide vapour into 98% " AnalaR " sulphuric acid under reduced pressure at room temperature. The latter was laboratory distilled water which, immediately before use, was redistilled from a little potassium permanganate and sodium hydroxide, precaution being taken to avoid contamination by spray.

A weighed amount of oleum was successively diluted with weighed amounts of water, and the specific conductivity was measured at each stage of the dilution. The precise composition of the oleum was calculated at the end of the series, it being assumed that the point of minimum conductivity corresponded to a composition represented by H_2SO_4.

The specific conductivity of the water–sulphur trioxide system about the region of sulphuric acid at 25° in ohms^{-1} cm.$^{-1}$.

Molality $H_2S_2O_7$	$10^3\kappa$	Molality $H_2S_2O_7$	$10^3\kappa$	Molality $H_2S_2O_7$	$10^3\kappa$	Molality H_2O	$10^3\kappa$
0·3059	2·233	0·0977	1·469	0·0349	1·161	0·0000	1·045
0·2971	2·210	0·0894	1·424	0·0272	1·124	0·0019	1·046
0·2729	2·136	0·0830	1·397	0·0193	1·091	0·0072	1·054
0·2400	2·031	0·0798	1·385	0·0113	1·064	0·0149	1·087
0·2004	1·893	0·0769	1·371	0·0000	1·045	0·0226	1·141
0·1591	1·735	0·0740	1·359			0·0376	1·298
0·1436	1·670	0·0661	1·318			0·0528	1·490
0·1263	1·598	0·0580	1·279			0·0846	1·941
0·1155	1·549	0·0502	1·240			0·1220	2·452
0·1066	1·509	0·0427	1·201			0·1608	2·950

This work was carried out during the tenure of a Salters' Fellowship (G. H.) and a D.S.I.R. maintenance grant (D. R. H.).

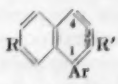
KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, March 31st*, 1955.]

1-*Phenylnaphthalenes.*

By F. G. Baddar, H. A. Fahim, and A. M. Fleifel.

[Reprint Order No. 6338.]

Contrary to Mitter and De (*J. Indian Chem. Soc.*, 1939, **16**, 199) the condensation of methylsuccinic anhydride with anisole in presence of aluminium chloride and nitrobenzene gave a mixture of β-*p*-methoxybenzoyl-α-methylpropionic acid and β-*p*-methoxybenzoylbutyric acid in the ratio of 13 : 1, respectively. The ratio of the β-methyl acid increased enormously when nitrobenzene was replaced by *s*-tetrachloroethane (cf. Baddar, Fahim, and Fleifel, *J.*, 1955, 2199). 7-Methoxy-2-methyl-1-tetralone gave with *o*-methoxyphenylmagnesium iodide (20 hours' refluxing), 3 : 4-dihydro-7-methoxy-1-*o*-methoxyphenyl-2-methylnaphthalene, which was dehydrogenated with selenium to 7-methoxy-1-*o*-methoxyphenyl-2-methylnaphthalene (I*a*). 2 : 7-Dimethyl-1-tetralone was similarly condensed with phenyl-, *p*-tolyl-, and *m*-tolyl-magnesium halide to give tertiary alcohols, which were dehydrated, then dehydrogenated with selenium to the naphthalenes (I*b*, *c*, and *d*), respectively. The low reactivity of the above tetralones towards Grignard



(I*a*) Ar = C_6H_4·OMe-*o*, R′ = Me, R = OMe
(I*b*) Ar = Ph, R′ = R = Me
(I*c*) Ar = C_6H_4·Me-*p*, R = R′ = Me
(I*d*) Ar = C_6H_4·Me-*m*, R = R′ = Me

reagents and the difficulty in dehydrating the resulting tertiary alcohols may be attributed to the $+I$ effect of the 2-methyl group.

2-Methoxy-1-*o*-methoxyphenylnaphthalene (I; R = H, R′ = OMe, Ar = C_6H_4·OMe-*o*) was prepared by decarboxylation of 1-(5-carboxy-2-methoxyphenyl)-2-methoxynaphthalene.

Experimental.—Condensation of methylsuccinic anhydride with anisole. The product (15 g., m. p. 110—136°) from methylsuccinic anhydride (11·4 g.), anisole (10 g.), and aluminium chloride (26·7 g.) in nitrobenzene (70 ml.) [cf. Mitter and De (*loc. cit.*)] was crystallised from glacial acetic acid, to give β-*p*-methoxybenzoyl-α-methylpropionic acid, m. p. 145—146°. Mitter and De (*loc. cit.*), and Mehta, Bokil, and Nargund (*J. Univ. Bombay*, 1943, **12**, *A*, 64) gave m. p. 144° and 141°, respectively.

The original acetic acid mother-liquor was evaporated in a vacuum to dryness, and the remaining oil (1·2 g.) was converted into β-*p*-methoxybenzoylbutyric acid semicarbazone, m. p. 179—180° (from ethanol), depressed to 145—157° on admixture with the semicarbazone of the α-methyl acid. Dhekne and Bhide (*J. Indian Chem. Soc.*, 1951, **28**, 504) gave m. p. 186°.

When nitrobenzene was replaced by *s*-tetrachloroethane the ratio of the α- to the β-methyl acid was 3 : 1. Both acids gave anisic acid on oxidation with 10% sodium hypobromite solution (cf. Baddar, Fahim, and Fleifel, *loc. cit.*).

3 : 4-*Dihydro*-7-*methoxy*-1-*o*-*methoxyphenyl*-2-*methylnaphthalene*. A solution of 2-methyl-7-methoxy-1-tetralone (3·8 g., 1 mol.) in dry thiophen-free benzene (30 ml.) was gradually added to an ethereal solution of *o*-methoxyphenylmagnesium iodide (from *o*-iodoanisole, 14·1 g., 3 mols.). Ether was driven off, and the mixture refluxed for 20 hr. and worked up as usual (cf. Baddar and El-Assal, *J.*, 1951, 1844). The product, b. p. 186—190°/6 mm., gave the *dihydronaphthalene* (56%), m. p. 57—58° (from ethanol) (Found: C, 81·4; H, 6·8; OMe, 23·5. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·1; OMe, 22·1%).

7-*Methoxy*-1-*o*-*methoxyphenyl*-2-*methylnaphthalene* (I*a*). This was prepared by heating the dihydro-compound with selenium powder at 330—340° for 3 hr. The *product* (40%) had b. p. 225—235°/10 mm., m. p. 68—69° (from dilute methanol) (Found: C, 81·0; H, 6·8; OMe, 24·4. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5; OMe, 22·3%).

3 : 4-*Dihydro*-2 : 7-*dimethyl*-1-*phenylnaphthalene*.—2 : 7-Dimethyl-1-tetralone was prepared in 84% yield by heating the corresponding butyric acid with 85% sulphuric acid for 1 hr. on the water-bath (cf. Mayer and Stamm, *Ber.*, 1923, **56**, 1424; Baker, MacOmie, and Warburton, *J.*, 1952, 2991). When this tetralone (3·5 g., 1 mol.) was condensed with phenylmagnesium iodide (3 mols.) as previously mentioned, it gave 3 : 4-*dihydro*-2 : 7-*dimethyl*-1-*phenylnaphthalene* (53%), b. p. 182—184°/7 mm., $n_D^{20} > 1·7$ (Found: C, 91·6; H, 7·6. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%).

2 : 7-*Dimethyl*-1-*phenylnaphthalene* (I*b*). This *hydrocarbon* was obtained by the dehydrogenation of the above dihydro-compound with selenium; it had b. p. 230—235°/10 mm., n_D^{30} 1·657 (Found : C, 92·7; H, 7·1. $C_{18}H_{16}$ requires C, 93·1; H, 6·9%). It failed to give either a solid mononitro-derivative or a stable adduct with 2 : 4 : 7-trinitrofluorenone or styphnic acid.

3 : 4-*Dihydro*-2 : 7-*dimethyl*-1-p-*tolylnaphthalene*. This was obtained as usual in 66% yield from 2 : 7-dimethyl-1-tetralone (3·5 g., 1 mol.) and *p*-tolylmagnesium iodide (3 mols.). The compound had b. p. 190—192°/7 mm., n_D^{30} >1·7 (Found : C, 89·6; H, 8·0. Calc. for $C_{19}H_{20}$: C, 91·9; H, 8·1%). It contained 0·07% of active hydrogen even after dehydration with potassium hydrogen sulphate.

2 : 7-*Dimethyl*-1-p-*tolylnaphthalene* (I*c*) was prepared by the dehydrogenation of the dihydro-compound with selenium, and had b. p. 215—220°/10 mm., n_D^{30} >1·7 (Found : C, 91·9; H, 7·4. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%).

3 : 4-Dihydro-2 : 7-dimethyl-1-*m*-tolylnaphthalene, obtained in 40% from 2 : 7-dimethyl-1-tetralone and *m*-tolylmagnesium bromide, had b. p. 166—170°/7 mm., n_D^{30} 1·5951 (Found : C, 90·0; H, 7·9%). The low carbon content may be due to incomplete dehydration of the alcohol. It gave 2 : 7-*dimethyl*-1-m-*tolylnaphthalene* (I*d*), b. p. 220—230°/7 mm., n_D^{30} >1·7, in 40% yield from the dihydro-compound as usual (Found : C, 91·6; H, 7·2%).

1-*Iodo*-2-*methoxynaphthalene*. This was obtained in 88% by iodination of 2-methoxynaphthalene (5 g., 1 mol.) with powdered iodine (8·4 g., 1·1 mols.) and yellow mercuric oxide (7·2 g., 1 mol.) in carbon tetrachloride (100 ml.) and acetic anhydride (3 ml.) at room temperature; it had m. p. 87—88°. Ray and Moomaw (*J. Amer. Chem. Soc.*, 1933, **55**, 3833) gave m. p. 88°.

1-(5-*Carboxy*-2-*methoxyphenyl*)-2-*methoxynaphthalene*. Methyl 3-iodo-4-methoxybenzoate (7·4 g., 1 mol.) was condensed with 1-iodo-2-methoxynaphthalene (7·2 g., 1 mol.) in presence of copper bronze (9·5 g.) at 230—235° for 5·5 hr. The product was worked up as usual, and the benzene-soluble *acid* formed needles, m. p. 243—244° (from methanol) (Found : C, 73·5; H, 5·4; OMe, 20·3. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2; OMe, 20·1%). The *methyl ester* had m. p. 179—180° (from methanol) (Found : C, 74·8; H, 5·5. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%).

The benzene-insoluble acid was methylated, to give *dimethyl* 2 : 2′-*dimethoxydiphenyl*-5 : 5′-*dicarboxylate*, m. p. 169—170° (from methanol), depressed on admixture with the above ester (Found : C, 65·7; H, 5·8; OMe, 36·6. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5; OMe, 37·6%).

2-*Methoxy*-1-o-*methoxyphenylnaphthalene*. This *ether* was prepared by heating the above acid (0·5 g.) with copper bronze (0·4 g.) in quinoline (5 ml.) at 210° for 2 hr. The product, b. p. 220—230°/6 mm. (0·25 g.), formed needles, m. p. 97—98°, from methanol (Found : C, 81·0; H, 6·1; OMe, 24·8. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1; OMe, 23·5%).

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The Mechanism of the Hydrolysis of Acetyl Chloride.

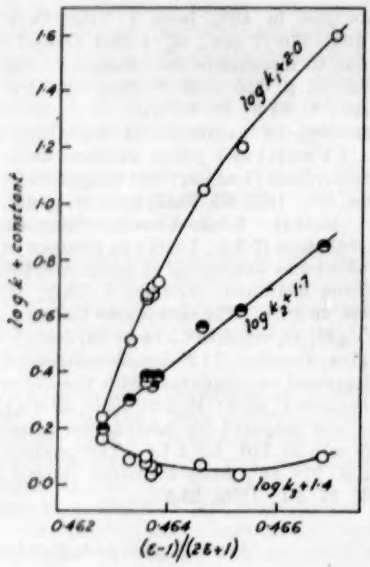
By V. GOLD and J. HILTON.

[Reprint Order No. 6342.]

IN a recent note Zimmerman and Yuan (*J. Amer. Chem. Soc.*, 1955, **77**, 332) reported measurements of the rate of hydrolysis of acetyl chloride in acetone containing small amounts of water. The velocity was found to be roughly proportional to the square of the water concentration, and the authors concluded from this that the reaction was termolecular, in agreement with views previously expressed by Swain (*ibid.*, 1948, **70**, 1124) and by Archer and Hudson (*J.*, 1950, 3259). Recently we tentatively proposed a bimolecular mechanism for this reaction in aqueous solution (*J.*, 1955, 838). We now show that Zimmerman and Yuan's results also support a bimolecular mechanism (for the hydrolysis in acetone–water) and that they cannot be regarded as unambiguous evidence for a termolecular mechanism.

It was pointed out by Bateman, Cooper, and Hughes (*J.*, 1940, 917; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603) that the apparent order of a reaction with respect to water in acetone solution need not reflect the molecularity of the reaction with respect to water and, for the same reason, we do not accept the validity of the conclusions drawn by Zimmerman and Yuan.

The inadequacy of their procedure can be regarded as being due to the large change in solvent properties which is caused by the addition of small amounts of water to acetone. This change is shown, for example, by the dielectric constant (Åkerlöf, *J. Amer. Chem. Soc.*, 1932, **54**, 4132). It is known that the rates of heterolytic reactions in mixed solvents vary with the composition of the solvent in a manner which is consistent with the hypothesis that the influence of solvent variation on the reaction rate is largely due to the change in the dielectric constant (Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, 1941, Chapter VIII). Hydrolysis reactions in which water is a reactant involve a separation of charges in the transition state—whatever the molecularity of the reaction (Gold, *Trans. Faraday Soc.*, 1948, **44**, 506)—and the rate coefficients are therefore expected to increase with the dielectric constant (ε) of the medium. If the simplest electrostatic theory can be applied to this type of reaction, log k should be a linear function of $(\varepsilon - 1)/(2\varepsilon + 1)$ (cf. Gold, Hilton, and Jefferson, *J.*, 1954, 2756). This treatment has been applied to rate measurements for a number of heterolytic reactions and the order of magnitude of the dielectric-constant dependence to be expected is therefore known (Cowan, McCabe, and Warner, *J. Amer. Chem. Soc.*, 1950, **72**, 1194).



We have accordingly examined the variation of the first-, second-, and third-order rate coefficients, calculated from Zimmerman and Yuan's data, as a function of dielectric constant. A plot of the logarithms of the three rate coefficients against $(\varepsilon - 1)/(2\varepsilon + 1)$ (a monotonic function of ε over the range of interest) is shown in the Figure. The dielectric constants used were derived by interpolation from Åkerlöf's measurements (*loc. cit.*) and the estimated uncertainties in this interpolation and of the experimental rate constants are indicated in the Figure by the size of the circles. It is found that the first- and the second-order rate coefficients show qualitatively the expected kind of dependence on dielectric constant. If linearity of the plot is taken as a criterion of mechanism (Archer and Hudson, *loc. cit.*; cf. Gold, Hilton, and Jefferson, *loc. cit.*) the bimolecular mechanism appears to be the most satisfactory. As there are other reasons why a unimolecular mechanism seems unlikely for this reaction in wet acetone, we conclude that, under these conditions, the hydrolysis of acetyl chloride is indeed bimolecular and that it is an example of hydrolysis for which the simple electrostatic treatment of dipole–dipole reactions is a good approximation.

Since there are no reactions of this kind for which a termolecular mechanism has been established beyond reasonable doubt, it is impossible to state categorically that the observed dependence of the third-order rate coefficient on dielectric constant might not be typical of the behaviour of termolecular rate coefficients. However, since reasonable models of a termolecular transition state still involve a structure of greater polarity than that of the reactant molecules, a termolecular rate coefficient is expected to increase with dielectric constant. We cannot, by any simple electrostatic treatment, account for the minimum in the curve of log k_3. In the light of these considerations, the termolecular mechanism appears to be the least satisfactory alternative considered.

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Prodigiosin.

By E. N. Morgan and (Miss) E. M. Tanner.

[Reprint Order No. 6383.]

Few details of the physical properties of purified prodigiosin have been recorded. Wrede and Hettche (*Ber.*, 1929, **62**, 2678) describe the free base as an amorphous mass, sintering between 70° and 80°. The perchlorate has a recorded m. p. of 228° (sintering at 226°). Hubbard and Rimington (*Biochem. J.*, 1950, **46**, 220) investigated the ultraviolet absorption of prodigiosin and of the perchlorate.

During the preparation of a sample for biological testing the purified base was obtained in lustrous, square pyramids, m. p. 151—152°, which were dark red with a green reflex. The ultraviolet absorption properties of the base and the infrared properties of both the base and the perchlorate are recorded below. The perchlorate had m. p. 227—229° undepressed by a sample of authentic prodigiosin perchlorate.

The essential features of the ultraviolet and visible spectrum of prodigiosin recorded by Hubbard and Rimington (*loc. cit.*) are confirmed by the results given below, except for the absence of bands around 250 mμ and the presence of several smaller bands. The striking change in colour from deep red in acid solution to the orange-yellow in alkaline solution is revealed in the intense narrow band at 541 mμ in the former and the broad, less intense band, centred at 468 mμ, in the latter. Neutral solutions (pH 7·4) in alcohol show the orange-yellow colour and the spectrum of alkaline solutions, together with a small band at 540 mμ indicating the presence of a small quantity of the red chromophore.

Experimental.—Crude prodigiosin, prepared by Commercial Solvents Corp. and made available to us through the courtesy of Dr. E. F. Elslager of Parke, Davis & Company, Detroit, U.S.A., was kept overnight at room temperature in methanol. After filtration, the dry pigment (2 g.) was dissolved in light petroleum (b. p. 60—80°) and chromatographed on an alumina column. The main scarlet band was removed mechanically and extracted with cold methanol. After concentration, the chilled extract deposited the pigment (1 g.). Recrystallisation from light petroleum (b. p. 60—80°) gave (slowly) square pyramids, m. p. 151—152° (Found: C, 73·9; H, 7·7; O, 5·5; N, 13·0. $C_{20}H_{25}ON_3$ requires C, 74·3; H, 7·8; O, 5·0; N, 13·0%).

Ultraviolet absorption in EtOH: (*a*) pH 7·4, max. at 225·5, 288·5, 337·0, 471·0, and 539·0 mμ (ε 10,810, 9820, 7590, 41,600, and 17,240 respectively); (*b*) pH 11, max. at 257·0, 281·0, 335·5, and 468·5 mμ (ε 7950, 9520, 7860, and 42,400 respectively); (*c*) pH 2·9, max. at 216·0, 296·0, 371·0, and 541·0 mμ (ε 8660, 12,220, 7750, and 132,200 respectively) and inflections at 275·0, 382·0, and 510·0 mμ (ε 6440, 7240, and 54,400 respectively).

Infrared spectrum (KBr discs): max. at 3270, 3235, 3070, 2895, 2835, 1622, 1578, 1557, 1543, 1458, 1430, 1373, 1360, 1336, 1277, 1253, 1198, 1185, 1144, 1136, 1115, 1078, 1054, 1030, 998, 957, 926, 907, 890, 844, 821, 806, 782, 767, 739, and 727 cm.$^{-1}$.

The perchlorate (Found: N, 9·9. Calc. for $C_{20}H_{25}ON_3,HClO_4$: N, 9·9%) (yield 80%) was undepressed on admixture with a sample of prodigiosin perchlorate originally prepared by Prof. Wrede, and supplied to us through the courtesy of Prof. C. Rimington, University College Hospital Medical School, London, to whom we express our gratitude.

Infrared spectrum (KBr discs): max. at 3310, 3240, 3085, 2910, 2845, 1622, 1605, 1517, 1455, 1465, 1379, 1337, 1315, 1297, 1285, 1264, 1242, 1202, 1150, 1129, 1119, 1094, 1080, 1066, 1043, 1012, 991, 962, 918, 885, 870, 862, 836, 822, 797, and 727 cm.$^{-1}$.

The ultraviolet absorption measurements were made on a Unicam SP500 Spectrophotometer, and the infrared spectra were obtained on a Grubb-Parsons S3A Spectrometer.

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[*Received, May 3rd, 1955.*]

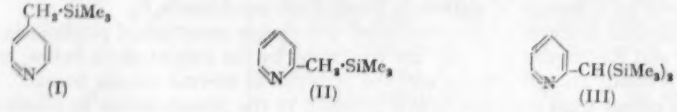
Organosilicon Compounds. Part XV. Derivatives of α- and γ-Picoline.*

By C. Eaborn and R. A. Shaw.

[Reprint Order No. 6387.]

In continuation of our study of organosilicon compounds derived by substitution at a reactive C–H bond (cf. *J.*, 1955, 1420), we have prepared 4- and 2-(trimethylsilylmethyl)-pyridine (I) and (II), and α-[bis(trimethylsilyl)methyl]pyridine (III). As expected from the acidities of the ω-hydrogen atoms of the parent picolines, the C–Si bonds are reactive in all three compounds, but distinctly least so in the disubstituted compound (III).

The 4-derivative (I) was completely cleaved (to γ-picoline and hexamethyldisiloxane) in 48 hr. by boiling aqueous ethanol; the 2-derivative (II) was more slowly cleaved, while



(I) (II) (III)

compound (III) was little changed in 20 hr. The same order of reactivity, (I) > (II) ⩾ (III), was found in alkaline and acidic cleavage. With 90% ethanol–water containing 5% of potassium hydroxide the base (I) was completely cleaved in ¼ hr. and the base (II) in 8 hr. at room temperature, while the disubstituted base (III) was only very slowly attacked at room temperature but was completely cleaved in 1 hr. at the boiling point. Aqueous 2N-hydrochloric acid at room temperature cleaved the base (I) in less than ½ hr., base (II) in 1½ hr., and base (III) in 16 hr.

If possible steric effects are neglected the greater reactivity in neutral and alkaline cleavage of the 4-derivative (I) compared with the 2-derivative (II) implies that the reactivity of the ω-hydrogen atoms is greater in γ- than in α-picoline (but see Bergstrom, *Chem. Rev.*, 1944, **35**, 85). The lower reactivity of the base (III) probably results from a combination of the electron release of the trimethylsilyl group and the steric hindrance it provides to solvation, both of which would lower the stability of the anion $2\text{-}Me_3Si\cdot\bar{C}H\cdot C_5H_4N$ and hence decrease the tendency of the ion to be formed in the cleavage reaction.

The easy acidic cleavage of the C–Si bond in the compounds no doubt follows protonation of the nitrogen atom, to give a positively charged entity in which the silicon atom is very susceptible to attack by the solvent. This is confirmed by the instability of the C–Si bonds of the picrates of bases (I) and (II), both of which are rapidly cleaved by ethanol. The lower reactivity of the disubstituted derivative (III) is again probably due to steric hindrance to solvation of the ion, $Me_3Si\cdot\bar{C}H\cdot C_5H_4\overset{+}{N}H$, formed in the cleavage. Steric hindrance also accounts for the inability of base (III) to form a picrate in dry ether, under which conditions bases (I) and (II) readily form such salts. An attempt to prepare the hydrochloride of the 4-derivative (I) by passing dry hydrogen chloride into its anhydrous ethereal solution led to cleavage with immediate precipitation of γ-picoline hydrochloride.

Replacement of the ω-hydrogen atoms of α-picoline by trimethylsilyl groups causes successive increase in the wavelength and the intensity of the main near-ultraviolet absorption maximum, while replacement of an ω-hydrogen atom of γ-picoline has little effect on the wavelength but decreases the intensity. The effects of the trimethylsilylmethyl group on the absorption of pyridine are in the same direction as, but are greater than, those of a similarly placed methyl group (Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26).

Experimental.—*2-(Trimethylsilylmethyl)pyridine and 2-[bis(trimethylsilyl)methyl]pyridine.* α-Picoline (102 g., 1·10 mole) in ether (100 ml.) was added to potassamide [prepared from

* Part XIV, *J.*, 1955, 2517.

potassium (41 g., 1·05 g.-atoms)] in liquid ammonia (1 l.). The ammonia was replaced by ether (750 ml.), and chlorotrimethylsilane (120 g., 1·10 moles) in ether (100 ml.) was added with stirring during 1½ hr. at such a rate as to keep the solution boiling gently. The mixture was boiled under reflux for 4 hr. and set aside overnight. Water was added and the ethereal layer was washed with water and then dried (Na_2SO_4). After removal of the ether the residue was fractionated in a glass-helices column (*ca.* 15 plates) to give α-picoline (29 g.), 2-(*trimethylsilylmethyl*)*pyridine* (II) (10·4 g., 6·7%), b. p. 191—192°, n_D^{26} 1·4866 (Found: C, 65·6; H, 9·3; N, 8·6; Si, 16·6. $C_9H_{15}NSi$ requires C, 65·4; H, 9·15; N, 8·5; Si, 17·0%), and 2-[*bis*(*trimethylsilyl*)*methyl*]*pyridine* (III) (16·4 g., 13·3%), b. p. 237—237·5°, n_D^{25} 1·4950 (Found: C, 60·6; H, 9·9. $C_{12}H_{23}NSi$ requires C, 60·7; H, 9·8%).

4-(*Trimethylsilylmethyl*)*pyridine*. To γ-picolylpotassium [prepared as for the α-analogue from potassium (60 g., 1·53 g.-atom), liquid ammonia, and γ-picoline (170 g., 1·83 moles)] in ether (1 l.), chlorotrimethylsilane (180 g., 1·62 mole) in ether (250 ml.) was added with stirring during 1½ hr. The mixture was boiled for 3 hr. and set aside overnight. By a procedure similar to that used for the α-compounds, but with fractionation in a spinning-band column there were obtained γ-picoline (98 g.) and 4-(*trimethylsilylmethyl*)*pyridine* (II) (26 g., 10·3%), b. p. 73—74°/4·5 mm., n_D^{24} 1·5000 (Found: C, 65·25; H, 9·15. $C_9H_{15}NSi$ requires C, 65·4; H, 9·15%), a colourless liquid which became yellow on exposure to air. A higher-boiling residue decomposed when attempts were made to fractionate it.

Picrates. Bases (I) and (II) with picric acid in ether gave, respectively, precipitates of 2-, m. p. 124° (Found: C, 45·9; H, 4·7; N, 14·0. $C_{15}H_{14}O_7N_4Si$ requires C, 45·7; H, 4·6; N, 14·2%), and 4-(*trimethylsilylmethyl*)*pyridine picrate*, m. p. 120° (Found: C, 45·9; H, 4·7%), in 75% yield. When these picrates were briefly boiled with ethanol and the solution was cooled, only 2-picoline picrate, m. p. and mixed m. p. 168°, and γ-picoline picrate, m. p. and mixed m. p. 165—166°, respectively, separated.

No precipitate was obtained in 2 months from a solution of the base (III) (0·98 g.) and picric acid (1·02 g.) in ether (175 ml.).

Neutral and alkaline cleavage. The course of these cleavages was followed by adding samples of the reaction mixture to water, in which the organosilylpicolines and hexamethyldisiloxane are insoluble but the parent picolines are soluble. The liquid which separated was washed with water and its refractive index was determined.

Boiling with 95% ethanol–water gave the following results:

Compound (I)		Compound (II)		Compound (III)	
Time (hr.)	n_D^{23}	Time (hr.)	n_D^{21}	Time (hr.)	n_D^{24}
0	1·5000 [(I)]	0	1·4873 [(II)]	0	1·4966 [(III)]
4	1·4220	2	1·4634	8	1·4924
7	1·4140	8	1·4315	20	1·4900
22	1·3920	24	1·4110		
48	1·3772 [$(Me_3Si)_2O$]				

The base (I) (1·82 g.) was boiled with 95% ethanol–water (2 ml.) for 48 hr., and excess of water was then added. The solution was saturated with sodium chloride, and the upper insoluble layer was washed with water, to give hexamethyldisiloxane (0·73 g., 82%), n_D^{24} 1·3768.

Treatment of the organosilicon bases with 90% ethanol–water containing 5% of potassium hydroxide at room temperature (*ca.* 18°) gave the following results:

Compound (I)		Compound (II)		Compound (III)	
Time, hr.	n_D^{23}	Time, hr.	n_D^{22}	Time, hr.	n_D^{22}
0	(1·5000) [(I)]	0	1·4874 [(II)]	0	1·4964 [(III)]
¼	1·3770 [$(Me_3Si)_2O$]	¼	1·4676	¼	1·4928
		2½	1·4080	2½	1·4880
		8	1·3778 [$(Me_3Si)_2O$]		

When the base (I) (0·82 g.) was added to the aqueous-alcoholic alkali (2 ml.) considerable heat was evolved. After ¼ hr. excess of saturated aqueous sodium chloride solution was added and the upper layer of liquid was separated and washed with water to give hexamethyldisiloxane (0·39 g., 96%), n_D^{22} 1·3760. The base (II), similarly treated for 8 hr., gave hexamethyldisiloxane in 81% yield.

The base (III) (0·62 g.), treated with the boiling aqueous alcoholic alkali (2 ml.) for 1 hr., gave hexamethyldisiloxane (0·38 g., 91%).

Acidic cleavage. The 4-derivative (I) (0·435 g.) gave a clear solution in 2N-aqueous hydrochloric acid (2·5 ml.) which quickly became cloudy, and an upper insoluble layer was formed. After ½ hr. this layer was separated, washed with water, and identified as hexamethyldisiloxane (0·20 g., 94%), b. p. 101°, n_D^{23} 1·3762.

The solution of the 2-derivative (II) in the same solvent remained clear for a longer period and hexaethyldisiloxane was obtained in 86% yield after 1½ hr. The solution of the disubstituted picoline (III) remained clear for much longer, but hexamethyldisiloxane was obtained in 92% yield after 16 hr.

Ultraviolet absorption spectra. These (see Table) were determined with a Unicam S.P. 500 Spectrophotometer, *n*-hexane being used as solvent. The maxima in the 220-mμ region

Base	$\lambda_{max.}$ (mμ) (ε in parentheses)			
4-(Trimethylsilylmethyl)pyridine	216·5 (8020)	252 (1320)	257 (1350)	—
2-(Trimethylsilylmethyl)pyridine	216 (7600)	264 (2920)	269 (3040)	276·5 * (2090)
2-[Bis(trimethylsilyl)methyl]pyridine ...	222 (11,700)	268·5 * (3350)	273·5 (3600)	280·5 * (2450)

* Inflexion.

probably corresponds with the maximum which is just below 200 mμ for pyridine (Pickett, Corning, Wieder, Semenov, and Buckley, *J. Amer. Chem. Soc.*, 1953, **75**, 1618). The most intense maxima in the 260 mμ region for α- and γ-picoline in *cyclo*hexane are at 262 (ε 2740) and 256 mμ (ε 1630), respectively (Herington, *loc. cit.*).

We thank the Director of the Chemical Research Laboratory, Teddington, for use of a spinning-band fractionating column.

(C. E.) University College, Leicester.
(R. A. S.) Birkbeck College, Malet St., London, W.C.1. [*Received, May 4th*, 1955.]

Quinoxalines and Related Compounds. Part II. The Preparation of NN′-Dimethyl-o-phenylenediamine and N-Methyl-o-phenylenediamine.*

By G. W. H. Cheeseman.

[Reprint Order No. 6395.]

The following three-stage synthesis of *NN′*-dimethyl-*o*-phenylenediamine has been described by Elderfield and Meyer (*J. Amer. Chem. Soc.*, 1954, **76**, 1887). *o*-Phenylenediamine was converted into *NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine which on treatment with methyl sulphate and alkali gave the *NN′*-dimethyl-diamide; hydrolysis with glacial acetic acid and concentrated sulphuric acid then furnished the *NN′*-dimethyldiamine in *ca.* 6% overall yield. It has now been found that the diamine can be obtained in excellent yield by the hydrolysis of the intermediate dimethyl compound with aqueous sulphuric acid. With this modification and Stetter's method (*Chem. Ber.*, 1953, **86**, 161) for the preparation of *NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine, *NN′*-dimethyl-*o*-phenylenediamine was obtained in 70% overall yield.

NNN′-Tritoluene-*p*-sulphonyl-*o*-phenylenediamine was obtained from the interaction of three mols. of toluene-*p*-sulphonyl chloride and one of *o*-phenylenediamine, or equimolar amounts of the chloride and *NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine. This derivative was converted into *NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine and *NN′*-dimethyl-*NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine by treatment with methyl sulphate and aqueous-methanolic sodium hydroxide. Methylation with methyl iodide and methanolic sodium methoxide yielded *N*-methyl-*NNN′*-tritoluene-*p*-sulphonyl-*o*-phenylenediamine which on hydrolysis with aqueous sulphuric acid gave *N*-methyl-*o*-phenylenediamine in high yield. Poorer yields of diamine were obtained from hydrolyses with concentrated sulphuric acid–acetic acid; acetylation and subsequent ring closure

* Part I, *J.*, 1955, 1804.

occurred and thus 1 : 2-dimethylbenziminazole was formed. The hydrolysis, by aqueous sulphuric acid, of *N*-methyl-*NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine, prepared from *NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine by Stetter's method (*loc. cit.*), also furnished *N*-methyl-*o*-phenylenediamine in high yield.

N-Methyl-*o*-phenylenediamine has been prepared from *o*-nitroaniline by a four-stage synthesis (Usherwood and Whiteley, *J.*, 1923, 1084; Phillips, *J.*, 1929, 2820; Cheeseman, *J.*, 1955, 1804). An alternative synthesis, based on *o*-chloronitrobenzene, involves two reactions under pressure (Elderfield and Meyer, *J. Amer. Chem. Soc.*, 1954, **76**, 1891). The three-stage preparation of the diamine now available from *o*-phenylenediamine *via* *NNN'*-tritoluene-*p*-sulphonyl-*o*-phenylenediamine and its *N*-methyl derivative was carried out in 43% overall yield and that *via* *NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine and its *N*-methyl derivative in 63% overall yield.

Experimental.—Pyridine was dried over potassium hydroxide and distilled.

NN'-*Ditoluene*-p-*sulphonyl*-o-*phenylenediamine*. This was prepared by Stetter's method (*loc. cit.*). The crude product was washed with water and heated under reflux with 96% ethanol (1 l.). After cooling, the diamide (153 g., 92%), m. p. 204—205°, was collected. Stetter gives m. p. 203° (corr.).

NN'-*Dimethyl*-NN'-*ditoluene*-p-*sulphonyl*-o-*phenylenediamine*. The above diamide (20·8 g., 0·05 mole) was boiled with 4N-sodium hydroxide (25 c.c., 0·1 mole). Methyl sulphate (9 c.c., 0·1 mole) was added to the cooled suspension and, after the initial reaction had moderated, the mixture was gently boiled for 5 min. After cooling, suspended solid was crushed and 4N-sodium hydroxide (25 c.c.) and methyl sulphate (9 c.c.) were added. The mixture was again boiled for 5 min. After two further similar treatments, the solid was filtered from the hot mixture and boiled with 0·75N-sodium hydroxide (400 c.c.). The alkali-insoluble material crystallised from 96% ethanol (375 c.c.) as colourless needles (19·7 g., 89%), m. p. 177—178°. Stetter (*loc. cit.*) gives m. p. 175° (corr.); Elderfield and Meyer (*J. Amer. Chem. Soc.*, 1954, **76**, 1887) give m. p. 178—179°.

NN'-*Dimethyl*-o-*phenylenediamine*. The dimethyl-diamide (22·2 g., 0·05 mole) was heated in concentrated sulphuric acid (20 c.c.) and water (2 c.c.) on the steam-bath for 4 hr., then poured into ice-water. 10N-Sodium hydroxide (100 c.c.) was added and the mixture diluted to *ca.* 1 l. to prevent the separation of sodium sulphate. Extraction with ether and evaporation of the dried (Na_2SO_4) extracts gave a dark oil which on distillation yielded *NN'*-dimethyl-*o*-phenylenediamine (5·85 g., 86%), b. p. 93°/1·7 mm., $n_D^{17\cdot5}$ 1·5955. This diamine readily crystallised as colourless needles, m. p. 31·5°; it discoloured on exposure to air. Elderfield and Meyer (*loc. cit.*) give b. p. 108·5—109°/5 mm., m. p. 30·5—31°, $n_D^{25\cdot5}$ 1·5914. The non-volatile fraction solidified and after two crystallisations from ethanol (charcoal) gave colourless needles of NN'-*dimethyl*-N-*toluene*-p-*sulphonyl*-o-*phenylenediamine*, m. p. 134—135° (Found: C, 62·4; H, 6·3; N, 9·8; S, 10·8. $C_{15}H_{18}O_2N_2S$ requires C, 62·05; H, 6·25; N, 9·65; S, 11·0%).

NNN'-*Tritoluene*-p-*sulphonyl*-o-*phenylenediamine*. (*a*) Toluene-*p*-sulphonyl chloride (172 g., 0·9 mole), *o*-phenylenediamine (32·4 g., 0·3 mole), and pyridine (150 c.c.) were heated on the steam-bath for 6½ hr. and then poured into excess of 2N-hydrochloric acid. The crude product gradually solidified and was filtered off, washed with water, and dried. Crystallisation from ethanol (4 l.) gave NNN'-*tritoluene*-p-*sulphonyl*-o-*phenylenediamine* (116 g., 68%) as needles, m. p. (mainly) 156—157°. The analytical sample, recrystallised from ethanol (30 parts), had m. p. 156—157° (Found: C, 56·8; H, 4·2; N, 5·1; S, 17·0. $C_{27}H_{26}O_6N_2S_3$ requires C, 56·8; H, 4·6; N, 4·9; S, 16·9%).

(*b*) Toluene-*p*-sulphonyl chloride (19·1 g., 0·1 mole), *NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine (41·6 g., 0·1 mole) and pyridine (50 c.c.) were heated on the steam-bath for 6½ hr. Colourless needles of *NNN'*-tritoluene-*p*-sulphonyl-*o*-phenylenediamine (39 g., 68%), m. p. and mixed m. p. 156—157°, were isolated as described under (*a*) above.

N-*Methyl*-NNN'-*tritoluene*-p-*sulphonyl*-o-*phenylenediamine*. The above tritoluene-*p*-sulphonyl compound (131·3 g., 0·23 mole), dissolved in sodium methoxide solution (1 equiv.), from sodium (5·29 g.) and dry methanol (1 l.), and methyl iodide (120 g.) were heated under reflux for 24 hr. The mixture was cooled and made alkaline with methanolic sodium methoxide (1 equiv.), and the crystalline precipitate of N-*methyl*-NNN'-*tritoluene*-p-*sulphonyl*-o-*phenylenediamine* (105 g., 78%), m. p. 200—202°, collected. Crystallisation from methanol (300 parts) gave colourless prisms, m. p. 202—203° (Found: C, 57·0; H, 4·85; N, 4·65; S, 16·1. $C_{28}H_{28}O_6N_2S_3$ requires C, 57·5; H, 4·8; N, 4·8; S, 16·45%). Acidification of the initial alkaline

filtrate with glacial acetic acid precipitated unchanged starting material (23 g., recovery 17·5%), m. p. (mainly) 156—157°.

N-Methyl-o-phenylenediamine. (*a*) The preceding methyl derivative (29·3 g., 0·05 mole) was dissolved in concentrated sulphuric acid (30 c.c.) and water (3 c.c.). The solution was heated on the steam-bath for 3½ hr. and the product isolated similarly to *NN'*-dimethyl-*o*-phenylenediamine above. Distillation gave *N*-methyl-*o*-phenylenediamine (5·0 g., 82%), b. p. 92—93°/1·7 mm., m. p. 22°, n_D^{17} 1·615; it discoloured on exposure to air. Elderfield and Meyer (*J. Amer. Chem. Soc.*, 1954, **76**, 1891) give b. p. 123—124°/10 mm., m. p.s 7·5—7·9° and 21—23°, $n_D^{20\cdot8}$ 1·6111. The diamine dihydrochloride was converted into 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline, m. p. and mixed m. p. 85·5—86·5°, by Kehrmann and Messinger's method (*Ber.*, 1892, **25**, 1629), and into 1 : 2-dimethylbenziminazole, m. p. and mixed m. p. 110·5—111·5°, by Phillips's method (*loc. cit.*) (Found : C, 74·3; H, 6·75. Calc. for $C_9H_{10}N_2$: C, 73·9; H, 6·9%).

(*b*) Hydrolysis of *N*-methyl-*NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine (21·5 g., 0·05 mole; Stetter, *loc. cit.*) with concentrated sulphuric acid (20 c.c.) and water (2 c.c.) for 4 hr. on the steam-bath similarly gave the diamine, b. p. 96—97·5/1·5 mm., m. p. 22°, $n_D^{18\cdot5}$ 1·6133, in 82% yield.

QUEEN ELIZABETH COLLEGE,
(UNIVERSITY OF LONDON), W.8.

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OBITUARY NOTICE.

JAMES FREDERICK SPENCER.

1881—1950.

JAMES FREDERICK SPENCER was born on February 8th, 1881, in Liverpool and died on December 31st, 1950. He received his education in Liverpool, proceeding from a private High School to the Victoria University, where he obtained his early chemical training. In 1901 he gained a First Class Honours Degree in Chemistry and was awarded a University Scholarship and the Leblanc Medal for technical chemistry. After a period of research in Liverpool with A. W. Titherley on the interaction of furfuraldehyde with sodium succinate, he obtained a Fellowship of the Victoria University in 1902, and a year later the award of an 1851 Exhibition Scholarship enabled him to study at the University of Breslau under R. Abegg for the Ph.D. degree. He obtained his Doctorate from that University in 1905 for a dissertation entitled "Die Beziehung zwischen Thalli-und Thalloverbindungen," which reported the results of his investigations into the oxidation–reduction potential of the thallous–thallic ion system in aqueous solutions of various thallium salts. The subsequent publication by Spencer and Abegg in the *Zeitschrift für anorganische Chemie* in 1905 is one of the classics of electrochemistry and includes some of the earliest studies of complex-ion formation and its effect on oxidation–reduction potentials.

Returning to England for the final year of his 1851 Exhibition, Spencer continued his researches at University College, London, working there with Sir William Ramsay. This was the period in which the Curies in France, and Ramsay, Rutherford, Soddy, and J. J. Thomson and their co-workers in England were carrying out their classic researches into radioactive changes and the nature of the electron. Ramsay and Spencer made a series of investigations into the effect of irradiating charged metal plates with ultraviolet light, the results of which were published in *The Philosophical Magazine* for 1906. In the light of present-day knowledge, and the enormous advances of the last fifty years, the paper makes interesting reading, as in it concepts accepted as commonplace today are seen slowly emerging at a period rich in discoveries.

In 1906 Spencer left University College on his appointment as Demonstrator, under Holland Crompton, in the Chemistry Department at Bedford College, London, then only eight years from its inauguration. Here he remained as Demonstrator, then Lecturer, and later Reader in Physical Chemistry, becoming head of the Department of Inorganic and Physical Chemistry in 1919 when the growing department was split into two parts, Holland Crompton remaining as head of the Department of Organic Chemistry and Director of the Chemical Laboratories. In 1927 Spencer was given the University title of Professor of Chemistry while retaining the headship of the Department of Inorganic and Physical Chemistry.

The period of his active life coincided with the expansion of women's higher education and he devoted himself wholeheartedly to promoting the interests of Bedford College. When he arrived as a junior member of staff, the chemistry department was small and he saw it grow from a mere handful of students into a flourishing school of chemistry. He gave unsparingly of his time to lecturing and developing practical courses and demonstrations for undergraduate classes, and over the years promoted and stimulated a variety of lines of postgraduate research among the small, but steadily maintained, number of postgraduate students who passed through his hands. Although he never married, he showed a truly paternal interest in the welfare of Bedford College, ever seeking methods by which he could enhance its academic reputation. He helped it not a little to its present-day status in the University. He undertook much work on committees within the University and the College and was at his best in this type of work, which he enjoyed. Thus, for a period he served as Chairman of the Board of Studies in Chemistry of the University; for several years as a member of the Council of Bedford College, on building committees at various epochs of its expansion and as a Governor of Marylebone Grammar School. On his retirement in 1946 he was appointed Emeritus Professor of Chemistry in the University and a Governor of Bedford College.

Spencer's research interests in chemistry covered a varied field. His early interest in organic chemistry was continued in the years from 1908—1910 when, with research students, he carried out a number of investigations into the reactions, in the absence of solvents, between magnesium and alkyl and aryl halider, in which products somewhat resembling Grignard

compounds were studied. An extension of this work to other metals included calcium and lithium and those of the aluminium group and the possible use of the methods for the preparation of hydrocarbons was pointed out.

In the years just before the first world war, Spencer returned to electrochemistry and the further investigation of the potentials of thallium ions, and developed the use of third-order electrodes for the measurement of electrode potentials, applying these to the determination of the solubility of sparingly soluble salts. In part of this work he was assisted by Miss Le Pla, who was a student of his, with whom he also developed a quantitative method for the separation of thallium from silver.

During the first world war he was unable to undertake active service owing to ill health, but, with Crompton, he undertook the preparation of some intermediates of drugs under the Royal Society War Committee.

Spencer then took up the study of the rare earths, applying the principles of the phase rule to separate ceric salts from the other rare-earth elements. This phase of his interests culminated in the publication of a monograph on "The Metals of the Rare Earths," which was the standard work on these elements for many years. His "Text Book of Practical Physical Chemistry" for students was written earlier and represented one of the first books of its kind for elementary students. It was a very good book in its time, a shorter version being used in the upper forms of schools for many years. In the course of developing practical physico-chemical methods for undergraduate students, his interest in practical techniques was shown in a number of improvements in physicochemical apparatus, and he developed a potentiometric method for the electrometric determination of copper in the presence of a number of other metals.

For very many years Spencer was the sole abstractor for the Chemical Society of the *Zeitschrift für physikalische Chemie*.

In the later years his attention turned to magnetochemistry and, assisted by his students, he carried out investigations into various aspects of the subject, including the study of alloy systems, of mixtures of liquids and of inorganic ions in solutions by the magnetochemical method. The school which he founded in this field still continues.

Outside of his work and academic career he maintained an interest in his family's small iron-foundry business, the existence of which did much to start him on his chemical career. His other main interest lay in philately, and he took much pleasure in his collection of British Commonwealth stamps.

All who worked with him will remember him for his kindliness and for the genuine goodwill with which he endeavoured to promote the interests of his department, the College, and the University, to which he devoted the greater part of his life.

V. C. G. Trew.
E. E. Turner.

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